DRUGS

DRUGS IN PALLIATIVE CARE

Andrew Dickman

A new edition of an essential pocket reference guide to prescribing for palliative care patients

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Drugs in Palliative Care

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THIRD EDITION

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Dedication

I would like to dedicate this book to my wife Victoria, for without her continued steadfast support during the recent difficult times many of us have experienced, this work would not have been possible.

I would like to thank James Baker for his timely contributions to this work.

Finally, I want to acknowledge and thank the two reviewers Penny Tuffin and Grace Ting for providing timely and critical feedback.

Foreword

Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided.

Paracelsus (1493–1541)
Swiss physician, alchemist, lay theologian, and philosopher

There are few fields of healthcare which do not, at some point, involve caring for the dying patient. Dying is the one clinical process that all people will face, yet the evidence base to inform how we look after our patients is woefully inadequate. This is not to say the medicines at our disposal are without evidence base; on the contrary, many have been rigorously evaluated in randomized clinical trials. However, such studies are usually conducted in patient populations with a better prognosis and performance status than those nearing the end of life. Patients under the care of generic and specialist palliative care services are rarely eligible for such studies and the clinical outcome measures used are often of limited utility in the palliative care context.

As healthcare practitioners, we need to embrace the concept of medicine being as much an art as a science; indeed, Sackett and colleagues' seminal editorial highlighted, 'The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.'[1] This is particularly apt in the practice of palliative care where we need to appraise the existing evidence and apply it, where possible, to the complexities of a patient with advanced disease who may have multiple comorbidities, polypharmacy, deranged biochemistry, and variable absorption and metabolism, all of which may be in an ever changing state of flux. To be able to do this requires a meticulous understanding of the complex pharmacokinetics and pharmacodynamics of the medicines commonly used by our specialty. I believe this book achieves this admirably.

Its author Dr Dickman is one of the most respected pharmacists in the field, with several practical palliative care books under his belt already. This new tome not only offers an evidence-based approach to the drugs commonly used in the management of palliative care patients, but this 'pharmacopedia' is also preceded by a thorough overview of the basic (and not so basic) science which underpins the clinical practice of pharmacology.

By remaining clinically active, Dr Dickman has never lost sight of producing a book which is of use to the practising medic, nurse, pharmacist, or other allied healthcare professional. This book is well suited as a reference for any profession involved in the care of the patient with incurable illness,

as well as a welcome informative addition to the practice of all ward-based and community staff.

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References

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence-based medicine: what it is and what it isn't. *BMJ*. 1996;*312*(7023):71–2.

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Symbols and abbreviations

♥	CredibleMeds® category: known risk of TdP
♡	CredibleMeds® category: possible risk of TdP
♡	CredibleMeds® category: conditional risk of TdP
	Drug only to be used under supervision of palliative care specialist
✢	unlicensed usage
	adverse effects
	dose
	pharmacology
⚠	warning
	cross-reference
	online reference
♀	female
♂	male
5-HT	5-hydroxytryptamine (or serotonin)
6-MAM	6-mono-acetylmorphine
6-MNA	6-methoxy-2-naphthyl acetic acid
7-OH-CBD	7-hydroxy cannabidiol
ABW	actual body weight
ACC	anterior cingulate cortex
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitor
ADH	antidiuretic hormone
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AGEP	acute generalized exanthematous pustulosis
AjBW	adjusted body weight
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine transaminase
ALT DIE	every other day (*alternus die*)
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
APM	Association for Palliative Medicine of Great Britain and Ireland
ARB	angiotensin receptor blocker
ASPCP	Association of Supportive and Palliative Care Pharmacy
AST	aspartate transaminase
BD	twice daily (*bis die*)
BNF	*British National Formulary*
BP	blood pressure
BPH	benign prostatic hyperplasia
BSA	body surface area
BSFS	Bristol Stool Form Scale
BTcP	breakthrough cancer pain
BUN	blood urea nitrogen
Ca^{2+}	calcium (ion)
CB	cannabinoid
CBD	cannabidiol
CBG	capillary blood glucose
CCK	cholecystokinin
CD	controlled drug
CD1	controlled drug—schedule 1
CD2	controlled drug—schedule 2
CD3	controlled drug—schedule 3
CD4a	controlled drug—schedule 4, part 1
CD4b	controlled drug—schedule 4, part 2
CD5	controlled drug—schedule 5
CEP	Certificate of Suitability
CGRP	calcitonin gene-related peptide
CH	Charrière
CHM	Commission on Human Medicines
CINV	chemotherapy-induced nausea and vomiting
CIPN	chemotherapy-induced peripheral neuropathy
CIVI	continuous intravenous infusion
cm	centimetre(s)
CNS	central nervous system
COPD	chronic obstructive pulmonary disease

COX-1	cyclo-oxygenase 1
COX-2	cyclo-oxygenase 2
CrCl	creatinine clearance
$CrCl_{adj}$	creatinine clearance adjusted for surface area
CSCI	continuous subcutaneous infusion
CTR	calcitonin receptor
CTZ	chemoreceptor trigger zone
CV	cardiovascular
CVA	cerebrovascular accident
CYP	cytochrome
DAT	dopamine reuptake transporter
DHCM	dihydrochloride monohydrate
DHT	dihydrotestosterone
DOAC	direct oral anticoagulant
DOR	delta opioid receptor
DRESS	drug reaction with eosinophilia and systemic symptoms
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition
DVLA	Driver and Vehicle Licensing Agency
DVT	deep vein thrombosis
EAPC	European Association for Palliative Care
e/c	enteric-coated
ECG	electrocardiogram
ECOG	European Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EM	extensive metabolizer
EMA	European Medicines Agency
EPS	extrapyramidal symptom
ESMO	European Society for Medical Oncology
FBC	full blood count
FDA	Food and Drug Administration
fL	femtolitre (equal to 10^{-15} litres)
Fr	French
G6PD	glucose-6-phosphate dehydrogenase
g	gram(s)
GABA	gamma-aminobutyric acid
GDP	guanosine diphosphate
GEP	gastroenteropancreatic
GFR	glomerular filtration rate
GFRABS	absolute glomerular filtration rate
GGT	gamma glutamyltransferase
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLU	5% glucose
GP	general practitioner
GPCR	G-protein-coupled receptor
GRK	GPCR kinase
GSL	general sales list (medicine)
GTP	guanosine triphosphate
GX	glycinexylidide
H^+	hydrogen ion (proton)
HbA1c	haemoglobin A1c (or glycated/glycosylated haemoglobin)
HDL	high-density lipoprotein
HER2	human epidermal growth factor 2
hERG	(cardiac) human ether-a-go-go related gene
HIV	human immunodeficiency virus
HMG-CoA	β-hydroxy β-methylglutaryl coenzyme
hr	hour
HR	heart rate (pulse)
HSS	hypersensitivity syndrome
IASP	International Association for the Study of Pain
IBW	ideal body weight
IM	intramuscular(ly)
InM	intermediate metabolizer
INR	international normalized ratio
IU	international unit(s)
IV	intravenous(ly)
IVI	intravenous infusion
K^+	potassium (ion)
kg	kilogram(s)
KOR	kappa opioid receptor
L	litre(s)
LAT1	L-type amino acid transporter-1
LDL	low-density lipoprotein
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LMWH	low-molecular weight heparin
LSD	lysergic acid diethylamide
MAD	mucosal atomization device
MAO-A	monoamine oxidase A

MAO-B	monoamine oxidase B
MAOI	monoamine oxidase inhibitor
MASCC	Multinational Association of Supportive Care in Cancer
MCH	mean cell haemoglobin
MCV	mean cell volume
MDMA	3,4-methylenedioxy methamphetamine ('ecstasy')
MDRD	Modification of Diet in Renal Disease
MEGX	monoethylglycine-xylidide
mg	milligram(s)
Mg^{2+}	magnesium (ion)
MHRA	Medicines and Healthcare products Regulatory Agency
micromol	micromole(s)
min	minute(s)
mL	millilitre(s)
mm	millimetre(s)
mmHg	millimetre(s) of mercury
mmol	millimole(s)
MOR	mu opioid receptor
MOR-NRI	MOR agonist–noradrenaline reuptake inhibitor
MRI	magnetic resonance imaging
ms	millisecond(s)
Na^{+}	sodium (ion)
Nac	nucleus accumbens
NaCl	sodium chloride injection BP (British Pharmacopoeia) 0.9% w/v
NAPQI	N-acetyl-p-benzoquinone imine
NAT2	N-acetyl transferase 2
NDMA	N-nitrosodimethylamine
NET	noradrenaline reuptake transporter
ng	nanogram(s)
NICE	National Institute for Health and Care Excellence
NK1	neurokinin 1
NMDA	N-methyl-D-aspartate
NMS	neuroleptic malignant syndrome
NO	nitric oxide
NOR	nociceptin receptor
NRI	noradrenaline reuptake inhibitor
NRLS	National Reporting and Learning System
NRT	nicotine replacement therapy
NSAID	non-steroidal anti-inflammatory drug
NVAF	non-valvular atrial fibrillation
NYHA	New York Heart Association
OCT	organic cation transporter
OD	once daily (*omni die*)
OHA	oral hypoglycaemic agent
OIBD	opioid-induced bowel dysfunction
OIC	opioid-induced constipation
OIH	opioid-induced hyperalgesia
OM	in the morning (*omni mane*)
ON	in the evening (*omni nocte*)
ORL-1	opioid-like receptor-1
OTC	over-the-counter
P	pharmacy only (medicine)
PAG	periaqueductal grey
PAH	polycyclic aromatic hydrocarbon
PAMORA	peripherally acting mu opioid receptor antagonist
PE	pulmonary embolism
PEG	percutaneous endoscopic gastrostomy
PFC	prefrontal cortex
pg	picogram(s) (equal to 10^{-12} grams)
P-gp	P-glycoprotein
PM	poor metabolizer
PO	orally (*per os*)
POM	prescription-only medicine
PONV	post-operative nausea and vomiting
PPI	proton pump inhibitor
PR	rectally (*per rectum*)
PRN	when necessary (*pro re nata*)
PT	prothrombin time
PTHrP	parathyroid hormone-related peptide
PVC	polyvinylchloride
QDS	four times daily (*quater die sumendus*)
QTc	QT corrected for heart rate
RANKL	receptor activator of nuclear factor kappa-B ligand
RBC	red blood cell (count)
REM	rapid eye movement
RINV	radiotherapy-induced nausea and vomiting
RR	respiratory rate

RVM	rostral ventromedial medulla
SeCr	serum creatinine
SERT	serotonin reuptake transporter
SGLT2	sodium–glucose co-transporter 2
SIADH	syndrome of inappropriate antidiuretic hormone hypersecretion
SLE	systemic lupus erythematosus
SmPC	summary of product characteristics
SNRI	serotonin–noradrenaline reuptake inhibitor
SS	serotonin syndrome
SSRI	selective serotonin reuptake inhibitor
SST	somatostatin
$SSTR_{1-5}$	somatostatin receptors (1 to 5)
ST	serotonin toxicity
SUBCUT	subcutaneous(ly)
SUBLING	sublingual(ly)
T4	thyroxine
TCA	tricyclic antidepressant
TD	transdermal
TdP	torsades de pointes
TDS	three times daily (*ter die sumendus*)
TENS	transcutaneous electrical nerve stimulation
THC	delta-9-tetrahydrocannabinol
TLR4	Toll-like receptor 4
TM	transmembrane
TNF	tumour necrosis factor
TRPV1	transient receptor potential cation channel subfamily V member 1
TSH	thyroid-stimulating hormone
U&Es	urea and electrolytes
UGT	uridine diphosphate glucuronosyltransferase
UM	ultrarapid metabolizer
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
v/v	volume by volume
WBC	white blood cell (count)
WFI	water for injections BP (British Pharmacopoeia)
WHO	World Health Organization
w/v	weight by volume

Chapter 1

Clinical pharmacology overview

Introduction

Interpatient variation is a substantial clinical problem when considering drug therapy. Examples of variation include failure to respond to treatment, increased incidence of adverse effects, and increased susceptibility to drug interactions. The concept of '*one dose fits all*' is clearly incorrect and is demonstrated by the unacceptable rate of hospital admissions caused by adverse drug reactions (approximately 5% in the UK; 7% in the US). This variation is hardly surprising, given all the factors that ultimately determine an individual's response to a drug (see Fig. 1.1).

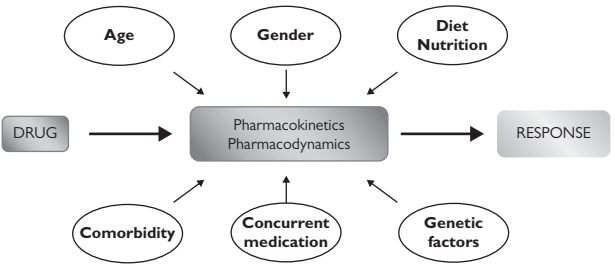


Fig. 1.1 Factors that influence an individual's response to drug therapy.

Pharmacokinetics

The rate and manner that a drug is absorbed, distributed, and eliminated are described by pharmacokinetics—in other words, *what the body does to the drug*.

Absorption

The bioavailability of a drug describes the proportion of the dose of a drug that enters the systemic circulation; for example, for intravenous (IV) morphine, this would be 100%, compared to 15 to 65% after oral administration.

For drugs taken orally that are intended for systemic action, a significant proportion of a given dose may not even enter the systemic circulation. This may be due to poor absorption from the gastrointestinal (GI) tract or metabolism in the gut wall or liver (called first-pass metabolism; see Box 1.1).

Box 1.1 First-pass metabolism

First-pass metabolism is a term used to describe the metabolism that occurs between the gut lumen and the systemic circulation. It can significantly reduce the bioavailability of a drug, such that oral administration is not feasible. Although gastric secretions inactivate certain drugs (e.g. insulin), the main sites of first-pass metabolism are the gut wall and liver.

The cytochrome P450 isoenzymes CYP3A4 and CYP3A5 (see Box 1.3), in addition to uridine diphosphate glucuronosyltransferases (UGTs), such as UGT2B7 (see Box 1.4), are located in the gut wall and liver. Many drugs are substrates of these isoenzymes and, as such, alterations in enteral cytochrome activity can significantly influence bioavailability. They are susceptible to inhibition and induction by a variety of drugs and foods. For example, one glass of grapefruit juice can cause significant inhibition of intestinal CYP3A4, whereas repeated consumption can interfere with hepatic CYP3A4. The majority of orally administered drugs must pass through the liver before entering the systemic circulation. Some drugs are susceptible to extensive first-pass metabolism, such that only a small proportion of the oral dose enters the systemic circulation, which renders oral administration impossible (e.g. lidocaine, fentanyl).

First-pass metabolism can be affected by disease, genetic influences, and enzyme inhibition or induction. This helps to explain the wide interpatient variation in drug absorption, and hence bioavailability of several drugs (e.g. morphine 15 to 65%).

Several transporter proteins present in the intestines influence the absorption of drugs. P-glycoprotein (P-gp) is an efflux transporter molecule that can affect the bioavailability of many drugs (see Box 1.2). Less well-categorized influx transporter proteins, such as organic cation transporters (OCTs), are also present and their activity may also be influenced by drugs and food.

Box 1.2 P-glycoprotein efflux transporter

P-glycoprotein (P-gp) is one of many protein transporters that can influence the bioavailability, distribution, and elimination of numerous drugs relevant to palliative care; for example, P-gp is believed to be a major determinant of the bioavailability of loperamide, morphine, and tramadol. It is found in the gastrointestinal tract, kidney, liver, and blood–brain barrier. There is wide patient variation because P-gp is genetically encoded and subject to polymorphism (see *Pharmacogenetics*, p. 15). Drug interactions can occur through induction or inhibition of P-gp, the clinical significance of which are being uncovered.

Distribution

Many drugs bind to plasma proteins such as albumin. Bound drug is inactive; only unbound drug is available to bind to receptors or cross cell membranes. Changes in protein binding can alter a drug's distribution, although this is rarely clinically important (an exception being phenytoin). P-gp is involved in the distribution of several drugs across the blood–brain barrier; for example, P-gp limits the entry of morphine into the brain.

Elimination

Various processes are involved in drug elimination, although hepatic and renal processes are the most important.

Drug metabolism

Many drugs are lipophilic, or non-polar, a property that allows them to readily cross cell membranes. Metabolism involves chemical reactions that produce compounds that are more hydrophilic, or polar, improving water solubility and aiding elimination in, for example, urine or bile.

Metabolism is conveniently divided into two phases: phase I—functionalization; and phase II—conjugation. Most drugs undergo phase I and II reactions, but some undergo either phase I or phase II metabolism. Phase I metabolism introduces, or exposes, a functional group through chemical reactions such as oxidation, reduction, or hydrolysis. These reactions are mainly catalysed by cytochrome P450 isoenzymes (see Box 1.3) located primarily in the liver, although other important sites include the GI tract (see *Absorption*, p. 3) and the brain. There are three possible results of phase I metabolism:

- complete loss of pharmacological activity (i.e. the metabolites are pharmacologically inactive)
- metabolites retain some pharmacological activity, but less than the parent drug
- the parent compound (prodrug) is pharmacologically inactive, but one or more metabolites are pharmacologically active.

Phase II metabolism involves conjugation reactions (such as glucuronidation or sulfation) affecting functional groups within the parent compound, or phase I metabolite(s). Uridine diphosphate glucuronosyltransferases

(UGTs) (see Box 1.4) are the main group of isoenzymes responsible for the glucuronidation of several drugs used in palliative care (e.g. morphine, diclofenac, haloperidol, and olanzapine). UGT2B7 is one of the most important human UGT isoenzymes with respect to drug clearance. Metabolites produced during phase II metabolism are generally pharmacologically inactive and more water-soluble than the parent compound. An important exception is morphine. One of its conjugated metabolites morphine-6-glucuronide is pharmacologically active and has been shown to be responsible for the analgesic effect of morphine.

Many drugs are dependent on cytochrome P450 isoenzymes for metabolism and/or elimination. Genetic variations or co-administration of inducers or inhibitors can lead to the development of significant toxicity or lack of effect, necessitating dose adjustments. The clinical significance of genetic variations or co-administration of inducers or inhibitors on the function of UGTs remains unclear for the majority of drugs.

Drug excretion

The main route of excretion of drugs is the kidney. Renal elimination is dependent on multiple factors that include:

- glomerular filtration rate (GFR)
- active tubular secretion (may involve P-gp)
- passive tubular secretion.

If a drug is metabolized to mainly inactive compounds (e.g. fentanyl), renal function will not greatly affect the elimination. If, however, the drug is excreted unchanged (e.g. pregabalin) or an active metabolite is excreted via the kidney (e.g. morphine), changes in renal function will influence the elimination and dose adjustments may be necessary.

Box 1.3 The cytochrome P450 system

The cytochrome P450 system consists of a large group of over 500 CYP enzymes that are involved in the metabolism of endogenous (e.g. steroids, eicosanoids) and exogenous (e.g. drugs) compounds. They are grouped according to amino acid sequence; a family is defined by >40% homology and a subfamily is defined by >55% homology. The five subfamilies CYP1A, CYP2C, CYP2D, CYP2E, and CYP3A have a major role in hepatic drug metabolism, with others having a lesser role. The list below briefly describes the CYP enzymes involved. Also see ➔ *Cytochrome P450 tables* on the inside back cover for a non-exhaustive list of substrates, inducers, and inhibitors, and ➔ *Glossary of common terms* for an explanation of terms used below. Each CYP enzyme displays multiple polymorphisms that give rise to several phenotypes, usually described as:

- poor metabolizer (PM)—absent or severely reduced metabolic capacity
- intermediate metabolizer (InM)—reduced metabolic capacity
- extensive metabolizer (EM)—normal metabolic capacity
- ultrarapid metabolizer (UM)—increased metabolic capacity.

(*Continued*)

Box 1.3 (*Contd.*)

CYP1A subfamily

- CYP1A1—mainly found in the lungs and metabolizes tobacco to potentially carcinogenic substances.
- CYP1A2—responsible for metabolism of approximately 15% of drugs that are metabolized by CYP enzymes. It is also involved in activation of procarcinogens. Although polymorphisms do exist, variations in CYP1A2 activity are largely due to non-genetic causes. For example, CYP1A2 is induced by tobacco smoke, cruciferous vegetables (e.g. broccoli, sprouts), grilled meat, and drugs such as omeprazole and carbamazepine. CYP1A2 activity may be inhibited by drugs, e.g. amiodarone, ciprofloxacin, diclofenac. Important substrates include olanzapine and theophylline.

CYP2A subfamily

- CYP2A6—metabolizes a small number of drugs, including nicotine and the prodrug tegafur. Also metabolizes tobacco to potentially carcinogenic substances. Polymorphisms exist, with 1% of the Caucasian population being PMs.

CYP2B subfamily

- CYP2B6—involved in the metabolism of an increasing number of drugs, including ketamine and methadone. Clopidogrel is a potential inhibitor, while tobacco smoke, rifampicin, and dexamethasone induce this CYP enzyme. Polymorphisms exist, but distribution and consequences remain undetermined.

CYP2C subfamily

- CYP2C8—a major hepatic cytochrome. Polymorphisms exist, but distribution and consequences remain undetermined. It is responsible for the metabolism of numerous drugs (e.g. amiodarone, olanzapine).
- CYP2C9—the most important of the CYP2C subfamily, responsible for metabolism of 10 to 20% of drugs, including warfarin, celecoxib, ibuprofen, diclofenac, and phenytoin. It is inhibited by several drugs, including fluconazole; rifampicin induces activity of CYP2C9. Polymorphisms exist and three phenotypes (PM, InM, EM) are described. Between 1% and 3% of Caucasians are PMs. Approximately 65% of Caucasians are considered EMs. Reduced activity of CYP2C9 can lead to unexpected NSAID toxicity. The PM phenotype is almost non-existent in the Asian population and affects roughly 10% of Africans.
- CYP2C19—involved in the metabolism of several drugs, including clopidogrel (prodrug), omeprazole, lansoprazole, diazepam, and citalopram. Inhibitors include modafinil, omeprazole, and fluoxetine. Carbamazepine can induce this CYP enzyme. Between 3% and 5% of Caucasians and Africans and up to 20% of Asians lack the CYP enzyme and are PMs. The UM phenotype may be present in up to 5% of Caucasians and Africans, but virtually non-existent in Asians.

Box 1.3 *(Contd.)*

CYP2D subfamily

- CYP2D6—this isoenzyme is responsible for the metabolism of approximately 25% of drugs, including codeine, tramadol, and tamoxifen. Inhibitors include paroxetine, levomepromazine, and celecoxib. Unlike the other isoenzymes, CYP2D6 cannot be induced. Many polymorphisms exist and four phenotypes have been identified: PM, InM, EM, and UM. About 5 to 10% of Caucasians are PMs and lack this isoenzyme. The incidence of PM in African populations is highly variable (from 0% to 20%), but rare in Asians (1%). Between 5% to 10% of Caucasians and up to 30% of Africans are UMs. Such a phenotype is extremely rare in Asians. Clinically important drug–drug interactions involving CYP2D6 occur because of the phenotype and/or co-administration of inhibitors.

CYP2E subfamily

- CYP2E1—has a minor role in drug metabolism. Its main importance is in paracetamol metabolism and potential toxicity. Polymorphisms exist, but the distribution and consequence remain undetermined.

CYP3A subfamily

This subfamily is the most abundant in the liver and is responsible for the metabolism of over 50% of drugs. There are four CYP3A genes, although only two are likely to be of importance in human adults. Nonetheless, these isoenzymes are so closely related that they are often referred to collectively as CYP3A. Polymorphisms exist, but the distribution and consequence remain undetermined.

- CYP3A4—the most significant isoenzyme involved in drug metabolism and frequently implicated in drug interactions. Although three phenotypes (PM, InM, UM) have been described, the activity of each allele is unknown and there is little genetic variation across ethnic groups. In fact, the causes of variations in activity are largely non-genetic. It is located mainly in the liver, but significant amounts are present in the gastrointestinal tract where it has an important role in first-pass metabolism. Indeed, the complex interaction between hepatic and intestinal isoenzyme levels helps to account for such wide variations in activity. There are several inducers (e.g. carbamazepine, rifampicin) and inhibitors (e.g. clarithromycin, grapefruit juice).
- CYP3A5—as with CYP3A4, three phenotypes have been described, loosely based on the system above (no metabolic capacity, reduced capacity, normal capacity). Interestingly, the 'no metabolic capacity' phenotype is the most common in the Caucasian (85%) and Asian populations (50%). About 20% of Africans and 10% of Asians, but <1% of Caucasians, are CYP3A5 'normal metabolizers'. CYP3A5 is also located in the liver and gastrointestinal tract, and has a similar substrate and inducer/inhibitor spectrum to CYP3A4. For transplant patients, the efficacy of ciclosporin and tacrolimus may well depend on the CYP3A5 phenotype, especially as the 'no metabolic activity' phenotype is the most common in Caucasian and Asian populations. Other substrates that can be affected by the CYP3A5 phenotype include alfentanil and midazolam.

Box 1.4 Uridine diphosphate glucuronosyltransferases

Uridine 5′-diphosphate glucuronosyltransferases (UGTs) are a superfamily of enzymes that perform phase II conjugative metabolism (glucuronidation). There are four families of UGTs in humans: UGT1, UGT2, UGT3, and UGT8. In total, there are 22 enzymes in these four families, but UGT1 and UGT2 comprise 19 and are involved in a range of clinically important drug interactions. Genetic variation in UGT function is thought to contribute to interindividual differences in drug response, as well as to the risk of certain diseases. The clinical significance, however, of genetic variation or inhibition/induction of UGTs currently remains unclear.

UGT1A family

- UGT1A1—involved in the elimination of bilirubin. Genetic variations are associated with unconjugated hyperbilirubinaemia in Gilbert's syndrome. It is involved in the conjugation of several drugs, including paracetamol and buprenorphine. Imatinib and ketoconazole act as inhibitors; enzalutamide is an inducer.
- UGT1A3—metabolizes several endogenous compounds such as oestrogens and vitamin D metabolites. Drug substrates include opioids (e.g. hydromorphone, buprenorphine, morphine) and non-steroidal anti-inflammatory drugs (e.g. etodolac, naproxen, ibuprofen).
- UGT1A4—has several endogenous substrates, including progestins, dihydrotestosterone, and 25-hydroxyvitamin D3. It is involved in the conjugation of several drugs, including amitriptyline, haloperidol, lamotrigine, midazolam, nicotine, and olanzapine. May be inhibited by sodium valproate and induced by, for example, carbamazepine, phenobarbital, phenytoin, and rifampicin.
- UGT1A6—involved in the metabolism of 5-HT. Drug substrates include paracetamol, naproxen, and tapentadol. May be induced by drugs such as carbamazepine and phenobarbital.
- UGT1A7—is an extrahepatic UGT, mainly expressed in the stomach. Involved in the metabolism of cannabidiol and S-lorazepam.
- UGT1A8—expressed in the colon. Substrates include morphine, tamoxifen, thyroxine, and valproate. May have a role in first-pass metabolism.
- UGT1A9—found in the liver and intestine. Likely to be the main UGT for ethanol glucuronidation and have a role in first-pass metabolism. Drug substrates include cannabidiol, diazepam, haloperidol, naproxen, nicotine, paracetamol, propofol, sorafenib, tapentadol, and valproate. Cannabidiol may be an inhibitor of UGT1A9.
- UGT1A10—is an extrahepatic UGT, expressed mainly in the intestine, and contributes to first-pass metabolism. Drug substrates include tamoxifen, thyroxine, and valproate.

UGT2B family

- UGT2B4—mainly located within the liver, this enzyme is involved in the metabolism of bile acids and androgen metabolites. Substrates include codeine, ibuprofen, lorazepam, midazolam, morphine, and oxycodone.

Box 1.4 *(Contd.)*

- UGT2B7—this enzyme is highly expressed in the liver and involved in the metabolism of a range of exogenous dietary and environmental compounds. Drug substrates include codeine, diazepam, diclofenac, haloperidol, hydromorphone, ibuprofen, lorazepam, midazolam, morphine, naproxen, oxycodone, tamoxifen, tapentadol, and valproate. Ketoconazole and cannabidiol may inhibit UGT2B7.
- UGT2B10—important enzyme in the glucuronidation of tobacco nitrosamines (including nicotine) and arachidonic acid metabolites. Drug substrates include amitriptyline and olanzapine.
- UGT2B15—important enzyme involved in the glucuronidation of androgens. Involved in the glucuronidation of numerous drugs, including diazepam, lorazepam, phenytoin, tamoxifen, and valproate. Valproate is believed to be an important inhibitor. UGT2B15*2, a variant that results in reduced activity, is believed to be present in approximately 50% of Caucasians, with only a slightly lesser prevalence in other populations.
- UGT2B17—shares over 95% homology with UGT2B15 and is also involved in the glucuronidation of androgens. Knowledge of drug substrates is limited; ibuprofen and megestrol are believed to be substrates.

Pharmacodynamics

The effect of a drug and how it works in terms of its interaction with a receptor or site of action are described by pharmacodynamics—in other words, *what the drug does to the body*.

Most drugs act upon proteins:

- receptor (e.g. morphine and μ-opioid receptor (MOR))
- ion channel (e.g. lidocaine and sodium (Na^+) channel, capsaicin and transient receptor potential cation channel subfamily V member 1 (TRPV1))
- enzyme (e.g. non-steroidal anti-inflammatory drug (NSAID) and cyclo-oxygenase)
- transporter complex (e.g. serotonin reuptake transporter (SERT) and selective serotonin reuptake inhibitors (SSRIs)).

Exceptions include antibiotics, cytotoxic drugs, and immunosuppressants. The term 'receptor' is used throughout the following to loosely describe the above protein targets. Note that an *autoreceptor* is a receptor that, upon binding a ligand (i.e. a substance that binds to a receptor), reduces the release of that ligand into the synapse; for example, presynaptic 5-HT_{1A} autoreceptors in the raphe nuclei reduce serotonin release through a negative feedback mechanism. A *heteroreceptor*, upon binding a ligand, mediates the release of other neurotransmitters.

Glossary of common terms

- *Agonists* are ligands that bind to, and activate, receptors to produce an effect.
- *Antagonists* are ligands that also bind to receptors but do not lead to activation. They may prevent the action of, or displace, an agonist.
- *Partial agonists* are ligands that activate receptors to a limited extent but may also interfere with the action of a full agonist. The circumstances in which a partial agonist may act as an antagonist or an agonist depend on both the efficacy (see below) of the drug and the pre-existing state of receptor occupation by an agonist; for example, buprenorphine will generally act as an antagonist if a patient is using excessive doses of morphine; at lower doses of morphine, buprenorphine will act as an agonist.
- *Biased agonism* or *functional selectivity* are terms used to describe the phenomenon whereby a ligand, after binding to a receptor, preferentially activates one of several cellular signalling pathways, whereas another agonist acting on the same receptor preferentially activates another pathway (see ➔ Chapter 1, *Opioid pharmacology*, p. 12 for more information).
- *Inverse agonist*—see Box 1.5.
- *Competitive antagonism* describes the situation that occurs when an antagonist competes with an agonist for the binding site of receptors. In such a situation, increasing the concentration of the agonist will favour agonist binding (and vice versa).
- *Irreversible competitive antagonism* can occur when the antagonist disassociates very slowly, or not at all, from receptors. Increasing the dose of the agonist does not reverse the situation.

- *Non-competitive (allosteric) antagonism* occurs when an antagonist blocks the effects of an agonist by interaction at some point other than the receptor binding site of the agonist.
- *Affinity* is a term used to describe the ability of a drug to bind to its receptors; for example, naloxone has a higher affinity for opioid receptors than morphine, hence its use in opioid toxicity.
- The *intrinsic activity* of a drug describes its ability to induce conformational changes in a receptor that induce receptor signalling. A drug may bind with high affinity but have low intrinsic activity. A drug with zero intrinsic activity is an antagonist.
- The *intrinsic efficacy* of a drug refers to the potential maximum activation of a receptor, and therefore desired response—that is, a full agonist has high intrinsic efficacy, a partial agonist has low to medium intrinsic efficacy, and an antagonist has zero intrinsic efficacy. For example, opioids with a low intrinsic efficacy (e.g. buprenorphine) must occupy more receptors to produce a given effect, compared to opioids with a higher intrinsic efficacy (e.g. fentanyl), and demonstrate a ceiling effect whereby larger doses of the drug do not produce a greater degree of analgesia because all the receptors are occupied.
- *Potency* refers to the amount of drug necessary to produce an effect; for example, fentanyl is more potent than morphine since the same analgesic effect occurs at much lower doses (micrograms vs milligrams). Potency depends not only on its affinity for the receptor and intrinsic efficacy, but also on pharmacokinetic variables that determine the quantity of the drug that is delivered to its site of receptor action.
- Very few drugs are specific for a particular receptor or site of action and most display a degree of *relative selectivity*. Selectivity refers to the degree by which a drug binds to a receptor, relative to other receptors. In general, as doses increase, the relative selectivity reduces, such that other pharmacological actions may occur, often manifesting as adverse effects.
- *Tolerance* is the decrease in therapeutic effect that may occur, over a period of time, by repeated doses of a drug (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).
- *Tachyphylaxis* is the rapid development of tolerance. It can occur with calcitonin, leading to rebound hypercalcaemia once the drug is discontinued.
- *Therapeutic index or margin* is the ratio between the dose producing undesired effects and the dose producing therapeutic effects. Drugs with narrow therapeutic margins are often implicated in drug interactions.
- *Polypharmacology* is a strategy that employs one or multiple drugs to interact with multiple molecular targets towards a specific outcome; for example, tapentadol is a μ-opioid agonist and noradrenaline reuptake inhibitor (NRI) and both effects contribute to its overall analgesic efficacy.

Box 1.5 Inverse agonism

The traditional receptor theory suggested that receptors are quiescent unless activated by a ligand that possesses both affinity and intrinsic efficacy (i.e. an agonist). Within this framework, ligands could act as agonists with various degrees of intrinsic efficacy, or as antagonists with zero intrinsic efficacy. Contemporary pharmacology, however, states that receptors can be *constitutively active*, i.e. display activity without binding with an agonist. In other words, receptors are constantly shifting between a range of active and inactive states. Examples include 5-HT_{2A} and 5-HT_{2C} receptors. As a result, a new class of ligand was discovered that can reduce the constitutive activity of a receptor. These ligands are called *inverse agonists*. They have negative intrinsic efficacy (i.e. decrease the constitutive activity of a receptor). Traditional antagonists, or *neutral antagonists*, by binding to the receptor, will antagonize both agonists and inverse agonists. Interestingly, most of the receptor antagonists in clinical use are actually inverse agonists. However, in most cases, since many receptors adopt an inactive state, there is no practical difference between a competitive antagonist and an inverse agonist.

Opioid pharmacology

Opioid receptors

Opioids are ligands that bind to one (or more) of the four discovered opioid receptors.

- The three classical opioid receptors are: μ (MOR), δ (DOR), and κ (KOR).
- Nociceptin receptor (NOR) (also called opioid-like receptor-1, or ORL-1, and is considered the non-opioid member of the opioid receptor family).

The different opioid receptors are distributed throughout the human body, which explains the wide range of pharmacological responses observed following administration of opioid agonists. Most clinically used opioids produce their major pharmacological effects through MORs. Although the MOR is the main target for opioid analgesics, the DOR, KOR, and NOR also regulate pain and analgesia and the relative affinities for these receptors contributes to each opioid analgesic's unique properties.

All four opioid receptors are G-protein-coupled receptors (GPCRs), which have a characteristic structure comprising seven transmembrane (7TM) α-helices, linked by three intracellular and three extracellular loops, with an extracellular N-terminal and an intracellular C-terminal domain. GPCRs are coupled with intracellular effector systems, primarily via an *inhibitory* G-protein. Each G-protein is a heterotrimer, composed of three subunits, namely Gα, Gβ, and Gγ. At rest, the G-protein is attached to guanosine diphosphate (GDP). When the receptor is activated by a ligand, conformational changes occur, allowing the conversion of GDP to guanosine triphosphate (GTP), which causes the heterotrimer to dissociate into Gα–GTP and Gβγ subunits. The now active subunits interact with numerous intracellular pathways. Activation of MOR and DOR results in

the opening of potassium channels and inhibition of adenylate cyclase and voltage-gated calcium channels, which lead to membrane hyperpolarization, reduced neuronal activity, and neurotransmitter release; activation of KOR inhibits calcium channels and neurotransmitter release.

Research has recently identified that the *MOR* gene can generate three classes of splice variants:

- a 7TM receptor
- a 1TM protein
- a 6TM receptor.

The 7TM receptor mediates analgesia, as described earlier. The 1TM protein does not bind to opioids but is believed to potentiate the action of opioids by enhancing the stability of 7TM receptors. The 6TM receptor is believed to bind to an *excitatory* G-protein, leading to an increased release of neurotransmitters and subsequent activation of NMDA receptors. Expression of the 6TM variant is believed to increase with continuous opioid exposure, something that has implications for tolerance and opioid-induced hyperalgesia (OIH).

Ligand binding also stimulates receptor phosphorylation by GPCR kinase (GRK), which can lead to recruitment of β-arrestins to the receptor. These are intracellular proteins that block the interaction between the receptor and the G-protein, and target the receptor for endocytosis. The net result is *homologous* receptor desensitization and internalization. β-arrestins are also believed to interact with different intracellular pathways, producing numerous downstream effects. Desensitized receptors recover over time; internalized receptors can then be either dephosphorylated and reinserted into the plasma membrane (resensitization) or trafficked to lysosomes for degradation (inactivation).

Biased agonism

It was previously assumed that one opioid agonist interaction with a given receptor differed from another only in terms of pharmacokinetics (e.g. absorption, distribution, elimination, and receptor binding and dissociation rates). Once bound to a receptor, it was thought that all opioid agonists for that receptor would engage in the same intracellular signalling pathways, resulting in the same intracellular responses, only differing from one another in the magnitude of those responses. Since the turn of the century, however, research has proven that this is too simplistic a model. Each opioid agonist interacts with its receptor in a unique way, which, in turn, alters the nature and balance of the responses elicited by the opioid agonist at that receptor. This phenomenon is referred to as *biased agonism* or *functional selectivity*.

Biased agonism has two key principles:

1. biased agonists stabilize receptor conformations that result in differential coupling to intracellular proteins
2. the response to GPCR activation (e.g. by an opioid agonist) arises from many cellular pathways; differential coupling to G-proteins, GRKs, and β-arrestins can preferentially activate one pathway over another.

This became of great significance for opioid agonists with ground-breaking research in 2005,[1] which reported that each opioid interacts with the

MOR and intracellular signalling pathways (i.e. G-protein and β-arrestin 2) in a specific fashion. It led to the novel concept that opioid analgesia via MOR is mediated via G-protein signalling, whereas respiratory depression, constipation, and opioid tolerance are mediated predominantly via β-arrestin-dependent signalling pathways. Subsequently, MOR ligands that do not recruit β-arrestin 2 to the receptor were developed, under the assumption that this would avoid these adverse effects while maintaining analgesia. The first G-protein-biased MOR agonist oliceridine produces comparable analgesia and has a favourable safety/tolerability profile in terms of respiratory and gastrointestinal adverse effects, compared to morphine. In August 2020, the Food and Drug Administration (FDA) approved its use for the management of moderate to severe acute pain. Nonetheless, it still does produce respiratory depression and constipation in a dose-dependent manner.

Despite much research effort devoted towards the development of novel G-protein-biased MOR agonists, it is still unclear which *in vivo* physiological responses are mediated by G-protein signalling and which responses are mediated by β-arrestin 2 signalling. A competing hypothesis suggests that the improved adverse effect profile of G-protein-biased MOR agonists, such as oliceridine, is due to low intrinsic efficacy[2]—similar, in fact, to that of buprenorphine, which interestingly displays bias against β-arrestin 2 recruitment and potentially less risk of respiratory depression and analgesic tolerance, compared with other opioids (although this may be related to its multiple receptor binding, rather than simply to low intrinsic efficacy at the MOR).

It is worth noting that the above describes a simplistic view. Opioid receptors reside in different neuronal structures throughout the body. Each structure will have distinct effector and regulatory mechanisms, thus making it difficult to interpret *in vitro* findings and elucidate exact receptor function *in vivo*. The situation is even more complicated because it is believed that opioid receptors may exist as dimers; for example, MOR and DOR can form a heterodimer receptor complex, which may behave in a way that is distinct from the constituent receptors. Each opioid therefore has a distinct pharmacological profile, dependent not only on the receptor(s) to which it binds and subsequent unique conformational changes in the receptor, but also on the intracellular pathways at its receptor(s) that it activates. This can explain the concept of incomplete cross-tolerance and forms the basis for opioid switch (see ➔ *Opioid-induced hyperalgesia and tolerance*, p. 51 and ➔ *Equianalgesia and opioid switch*, p. 56). Taken together with differences in pharmacokinetics and genetic variation, it is no wonder that many facets of opioid pharmacology remain unknown.

Pharmacogenetics

> If it were not for the great variability among individuals, medicine might as well be a science and not an art.
>
> Sir William Osler, 1892

In the middle of the last century, two adverse drug reactions were described as being caused by genetic mechanisms. G6PD deficiency and pseudocholinesterase deficiency were shown to be manifestations of specific gene mutations. In 1959, the term 'pharmacogenetics' was introduced. It was only towards the end of the last century that significant advances were made. As a result of the human genome project, a broader term 'pharmacogenomics' was introduced (see Box 1.6).

Box 1.6 Basic genetic concepts

The human genome consists of 23 pairs of chromosomes (or 22 pairs of *autosomes* and one pair of sex-linked chromosomes), within which are sequences of DNA that are referred to as *genes*. With the exception of the sex-linked X- and Y-chromosomes, an individual inherits two copies of each gene, one from each parent. A gene can exist in various forms, or *alleles*. *Wild-type* is the most common active allele. Only 3% of the human genome encodes proteins.

An individual's inherited genetic profile, or *genotype*, may be described as being:

- homozygous dominant (i.e. a specific gene consists of two identical dominant alleles)
- heterozygous (i.e. a specific gene consists of two different alleles, one usually being dominant and the other recessive)
- homozygous recessive (i.e. a specific gene consists of two identical recessive alleles).

An individual's *phenotype* describes the observable characteristics that are a result of the genotype and environment. Particular inherited phenotypical traits may be described as being *autosomal dominant* or *recessive*.

Pharmacogenetics is the study of how variation in an individual gene affects the response to drugs which can lead to adverse drug reactions, drug toxicity, therapeutic failure, and drug interactions.

Pharmacogenomics is the study of how a patient's genome can influence how they respond to drug therapy.

Variations can exist in a population for the DNA that encodes a protein. The simplest form of variations are *single-nucleotide polymorphisms*, in which a certain part of a gene differs by only one nucleotide. If a variation occurs in at least 1% of the population, then this is referred to as a *genetic polymorphism* (i.e. differences in DNA sequences). In most regions of the genome, a polymorphism is of little clinical consequence. However, a polymorphism in a critical coding or non-coding region can lead to altered protein synthesis, with clinical implications such as abnormal drug responses.

Genetic variability can affect an individual's response to drug treatment by influencing pharmacokinetic and pharmacodynamic processes; for example, variations in genes that encode cytochrome P450 isoenzymes, drug receptors, or transport proteins can determine clinical response. Pharmacogenetics can aid in the optimization of drug therapy through the identification of individuals who are likely to respond to treatment or those who are most likely at risk of an adverse drug reaction. Although the exact proportion of adverse drug reactions caused by genetic variability is unclear, emerging evidence suggests an increasing role. Pharmacogenetic testing is currently in early development, but current examples include:

- the need for human epidermal growth factor 2 (HER2) testing before initiating trastuzumab (Herceptin®) therapy
- genetic testing of Han Chinese recommended for patients before commencing carbamazepine therapy due to an association between toxic skin reactions and a specific genotype.

Pharmacogenetic testing has the potential to improve the safety and efficacy of several drugs commonly encountered in palliative care, e.g. analgesics, antidepressants, antipsychotics.

Genetic influences on pharmacokinetics

Variations in genes that encode transport proteins have been implicated in altered therapeutic responses; for example, P-gp polymorphisms have been associated with altered morphine analgesia. However, the characterization and implications of transporter protein variations are less developed, when compared to drug metabolism. There is no doubt that polymorphism of metabolic enzymes has a great effect on interpatient variability. Several polymorphisms that affect drug metabolism have been identified and there is substantial ethnic variation in distribution. Functional changes, because of a polymorphism, can have profound effects, including:

- adverse drug reaction
- toxicity
- lack of effect
- drug interaction.

Genetic polymorphisms of cytochrome P450 isoenzymes can be divided into four phenotypes, although not all polymorphisms exist for all isoenzymes (see Box 1.3):

- *Poor metabolizers* (PMs) have two non-functional alleles and cannot metabolize substrates.
- *Intermediate metabolizers* (InMs) have one non-functional allele and one low-activity allele, so they metabolize substrates at a low rate.
- *Extensive metabolizers* (EMs) have one or two copies of a functional allele and metabolize substrates at a normal rate.
- *Ultrarapid metabolizers* (UMs) have three or more copies of a functional allele and metabolize substrates at an accelerated rate.

The isoenzymes CYP2C9, CYP2C19, and CYP2D6 are responsible for approximately 40% of cytochrome P450-mediated drug metabolism. They display high levels of polymorphism which have been shown to affect the response of individuals to many drugs (see Box 1.7). Pharmaceutical

manufacturers have realized the importance of pharmacogenetics; fewer drugs will be developed that are affected by pharmacogenetic factors because potential agents will be discarded at an early stage of development.

The consequences of a particular phenotype depend upon the activity of the drug. PMs are at increased risk of therapeutic failure (through poor

Box 1.7 Examples of the effect P450 polymorphisms have on selected drugs

- Codeine—needs to be metabolized by CYP2D6 to morphine before analgesia is observed. PMs derive no analgesia from codeine. Drugs that inhibit CYP2D6 will mimic the PM phenotype, interacting with codeine to result in no analgesia. UMs are at risk of life-threatening adverse drug reactions as codeine is metabolized at a very high rate.
- Methadone—shows complex pharmacology. Mainly metabolized by CYP3A4/5, but CYP2B6 and CYP2D6 are also involved. PMs of CYP2B6 and CYP2D6 are at risk of developing toxicity if methadone is titrated too quickly.
- Non-steroidal anti-inflammatory drugs (NSAIDs)—specific genotypes that reduce the activity of CYP2C9 can lead to unexpected toxicity with some NSAIDs, e.g. celecoxib.
- Tamoxifen—the active metabolite endoxifen is produced by a reaction involving CYP2D6. Patients with a PM phenotype are at risk of therapeutic failure with tamoxifen. Drugs that inhibit CYP2D6 will also mimic the PM phenotype and should be avoided when taking tamoxifen.
- Theophylline—the metabolism of theophylline is highly dependent on CYP1A2 activity, which varies with specific genotypes.
- Tramadol—is primarily metabolized by CYP2D6 to an active compound *O*-desmethyltramadol (M1), which is a more potent opioid agonist. PMs show a poor response to tramadol. As with codeine, drugs that inhibit CYP2D6 can mimic the PM phenotype.

metabolism to an active compound) or adverse effects (due to accumulation). In contrast, UMs are at increased risk of therapeutic failure with conventional doses due to excessive metabolism; in the case of a prodrug, rapid production of the active compound could lead to toxicity. For example, a patient with a UM phenotype for CYP2D6 may rapidly convert codeine to morphine, increasing the risk of developing toxicity; a patient with PM status for CYP2D6 will derive little, if any, analgesic benefit from codeine.

Genetic influences on pharmacodynamics

Genetic polymorphisms of drug receptors, or disease-related pathways, can influence the pharmacodynamic action of a drug. These are generally less well categorized than pharmacokinetic consequences. Nonetheless, genetic variations have been shown to be clinically relevant for morphine analgesia and antidepressant therapy. In the latter case, associations between

serotonin transport gene polymorphisms and depression have been demonstrated. It has also been shown that genotyping for polymorphisms of certain serotonin or noradrenaline pathways can inform the clinical choice of antidepressant; for example, a patient who fails to respond to citalopram (SSRI) could, in fact, respond to reboxetine (NRI).

Hepatic impairment

Impaired hepatic function can affect the pharmacokinetics of many drugs through effects on absorption, distribution, metabolism, and excretion. Absorption of drugs can be increased if intrahepatic shunts develop, routing drugs away from hepatocytes, and therefore reducing first-pass metabolism. Cholestasis can result in reduced absorption of lipophilic drugs that are dependent on bile salts, although this is likely to be of limited clinical significance. Distribution of certain drugs can be affected by reduced synthesis of albumin or the presence of increased bilirubin plasma levels which can affect protein binding, potentially leading to increased unbound drug levels and exposure. Phase I enzymes are generally considered to be more affected in hepatic disease, compared to phase II enzymes. In particular, activities of several CYP isoenzymes involved in phase I metabolism (CYP1A1, CYP2C19, and CYP3A4/5) appear to be more susceptible to the effects of hepatic disease than other isoenzymes (CYP2D6, CYP2C9, and CYP2E1). Hence, drugs metabolized by affected isoenzymes are expected to require dosage adjustments (i.e. dose reductions and/or increased dose intervals) in patients with hepatic impairment. Phase II metabolism by UGT enzymes appears to be preserved in mild to moderate hepatic impairment, although possibly less so in severe impairment. Hepatic impairment can affect the renal excretion of drugs and metabolites by decreasing renal blood flow and glomerular filtration rate. Similarly, cholestasis can affect the biliary excretion of drugs and metabolites, an effect that can also impact on drugs that undergo enterohepatic recirculation. In terms of pharmacodynamics, hepatic impairment can cause reduced activity of P-gp at the blood–brain barrier, leading to increased permeability to certain drugs and subsequent central nervous system (CNS) activity.

Unlike impaired renal function, there is no simple test that can determine the impact of liver disease on drug handling, or guide dose selection. Several factors need to be considered before such impact can be assessed:

- Does the patient have decompensated cirrhosis (characterized by ascites, hepatic encephalopathy, hepatorenal syndrome, jaundice, and variceal bleeding)?
- What is the patient's synthetic function like (e.g. albumin, bilirubin, international normalized ratio (INR), prothrombin time (PT))?
- What is the trend in the patient's liver function tests (LFTs) (see Table 1.1)?

Clinical scores, such as the Child–Pugh scoring system, act as a surrogate for drug clearance, although it was developed to predict disease severity and patient outcome (see Table 1.2). This system is based on three objective measures (serum bilirubin, serum albumin, PT/INR) and two subjective measures (presence of encephalopathy and ascites). Hepatic impairment is classified as mild (class A), moderate (class B), or severe (class C). While this system does offer some guidance for dose adjustment, it lacks the specificity to quantify the ability of the liver to metabolize drugs. In general, the metabolism of drugs is unlikely to be affected unless the patient has severe liver disease. Most problems are seen in patients with jaundice, ascites, and

Table 1.1 Common liver function tests

Liver function test	Comment
Albumin	Synthesized in the liver. Low plasma levels are indicative of chronic liver impairment. There are other causes of low albumin, e.g. malnutrition, malignancy, nephrotic syndrome
ALP	Produced by several tissues, including the bile ducts and bone. Elevated levels are indicative of biliary damage. Other causes of raised ALP include bone metastases, healing fracture, and hyperthyroidism
ALT AST	ALT and AST are present in hepatocytes. Elevated levels indicate inflammation and damage to hepatocytes. ALT is more specific to the liver, since AST levels can also be high because of myocardial or skeletal muscle damage
Bilirubin	Bilirubin is the product of haemoglobin metabolism. Elevated levels are indicative of hepatic impairment or biliary obstruction. Haemolytic anaemia can also lead to elevated bilirubin levels. Typically, total bilirubin (both conjugated and unconjugated) level is measured. Elevated conjugated bilirubin levels are suggestive of cholestasis, whereas elevated unconjugated levels are suggestive of hepatic impairment
GGT	The level rises in hepatobiliary disorders, particularly cholestasis (in tandem with ALP level). Elevated levels can also occur with high alcohol intake and certain CYP450 enzyme-inducing drugs
INR/PT	Both represent a useful measure of the synthetic ability of the liver. Abnormalities can be a sensitive marker of hepatic impairment but can also occur in chronic liver impairment. Both are dependent on a vitamin K-derived clotting factor. Vitamin K deficiency (e.g. cholestasis, malnutrition) can present a false impression of reduced synthetic capability

LFT, liver function test; ALP, alkaline phosphatase; ALT, alanine transaminase; AST; aspartate transaminase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; PT, prothrombin time.

hepatic encephalopathy. As such, doses of drugs should be reviewed in the following situations:

- hepatically metabolized drug with a narrow therapeutic index
- renally excreted drug with a narrow therapeutic index
- significant involvement of the cytochrome P450 system (CYP3A4/5 is highly susceptible to liver disease, whereas CYP2D6 appears relatively refractory) in drug metabolism
- INR >1.2
- bilirubin >100micromol/L
- albumin <30g/L
- signs of ascites and/or encephalopathy.

Where possible, dosage amendments will be discussed in each monograph.

Table 1.2 Child–Pugh scoring system

Score indicator	1	2	3
Bilirubin (micromol/L)	<35	35–50	>50
Albumin (g/L)	>35	28–35	<28
INR (PT)	<1.7 (<4)	1.8–2.3 (4–6)	>2.3 (>6)
Encephalopathy	None	Grades 1–2	Grades 3–4
Ascites	None	Mild to moderate	Severe or intractable

Child–Pugh A (well compensated): 5–6 points
Child–Pugh B (significant impairment): 7–9 points
Child–Pugh C (decompensated): 10–15 points

Adapted from *Br J Surg*, **60**(8), Pugh RN, Murray-Lyon IM, Dawson JL, *et al.*, Transection of the oesophagus for bleeding oesophageal varices, pp. 646–9, Copyright (1973), with permission from Oxford University Press.

Renal impairment

Elimination of many drugs and metabolites is dependent upon renal function. Impaired renal function, coupled with rising urea plasma concentrations, induces changes in drug pharmacokinetics and pharmacodynamics. Implications for drug therapy include:

- increased risk of adverse effects and toxicity through reduced excretion of the drug and/or metabolite(s), e.g. pregabalin, morphine
- increased sensitivity to drug effects, irrespective of the route of elimination, e.g. antipsychotics
- increased risk of further renal impairment, e.g. NSAIDs.

Many of these problems can be avoided by simple adjustment of daily dose or frequency of administration. In other situations, however, an alternative drug may need to be chosen. It is worth noting that patients with end-stage renal disease may be at risk of increased drug toxicity due to the reduced activity of CYP3A4/5 and CYP2D6.

Estimating renal function

Unlike liver impairment, the impact of declining renal function is quantifiable. Accurate methods of determining renal function, or glomerular filtration rate (GFR), are unsuitable for routine clinical use. *Serum creatinine* (creatinine is a product of muscle metabolism) has been used as a simple tool to estimate GFR. However, there are serious limitations to this approach.

- As renal function deteriorates, serum creatinine concentration increases. However, many patients may have reduced GFR, but serum creatinine concentrations fall within the conventional laboratory normal ranges; for example, an increase from 50micromol/L to 100micromol/L is still within normal limits, even though renal function has clearly deteriorated.
- Renal function declines with age, but serum creatinine concentration generally remains stable. Thus, a 75-year old may have the same serum creatinine concentration as a 25-year old, despite having reduced renal function.

Creatinine clearance (CrCl) serves as a surrogate for GFR. The majority of dosage adjustment guidelines in the monographs are based upon CrCl. It can be determined from the Cockroft and Gault equation (see Box 1.8), which takes weight, age, gender, and serum creatinine into consideration. The original study was based on data from 249 male patients with stable renal function. Although the study used actual body weight (ABW), the authors acknowledged a correction factor should be used in patients with marked obesity or ascites. Thus, there are limitations with this method as it may report inaccurately for obese patients. In addition, serum creatinine may underestimate renal function in patients with hepatic impairment for several reasons, including reduced production of creatine (the precursor of creatinine) and interference with the analysis by elevated serum bilirubin concentration.

The original Cockcroft and Gault equation has been modified to use ideal body weight (IBW):

$$\text{IBW} = 2.3\text{kg} \times \text{each inch over 5ft} + \text{W}$$

(where W = 50kg for males and 45.5kg for females)

If a patient's ABW is less than his or her IBW, then ABW should be used. However, if the patient is obese, then a correction is used. The adjusted body weight (AjBW) correction states that if a patient's ABW is 30% over his or her IBW, then a 40% correction factor should be applied, and that weight should be used in the Cockcroft and Gault equation.

$$AjBW = 0.4(ABW - IBW) + IBW$$

A useful online calculator can be used to determine CrCl across a range of body weights, available from: https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation.

Box 1.8 Cockcroft and Gault equation for calculating creatinine clearance

$$CrCl = \frac{[(140 - age)\ (weight\ in\ kg)\ F]}{SeCr\ in\ micromol/L}$$

where F = 1.23 (male); 1.04 (female).

In the UK, renal function is increasingly being reported in terms of *estimated GFR* (e*GFR*), normalized to a body surface area of 1.73m^2. The formula used to calculate eGFR was derived from the Modification of Diet in Renal Disease (MDRD) study. The eGFR assumes the patient is of average size (assuming an average body surface area of 1.73m^2), allowing a figure to be determined using only serum creatinine, age, gender, and ethnic origin. It is primarily a tool for determining renal function, of which five categories have been described (see Table 1.3).

The eGFR is only an estimate of the GFR and has not been validated for use in the following groups or clinical scenarios:

- children (<18 years of age)
- acute renal failure
- pregnancy
- oedematous states
- muscle wasting disease states
- amputees
- malnourished patients.

Table 1.3 Stages of renal failure

Stage	eGFR (mL/min/1.73m^2)
1 (normal GFR)*	>90
2 (mild impairment)*	60–89
3 (moderate impairment)	30–59
4 (severe impairment)	15–29
5 (established renal failure)	<15

* The terms stage 1 and stage 2 chronic kidney disease are only applied when there are structural or functional abnormalities. If there are no such abnormalities, an eGFR of ≥60mL/min/1.73m^2 is regarded as normal.

While the eGFR may be used to determine dosage adjustments in the place of CrCl for most drugs in patients of average build, this is likely to produce erroneous results in palliative care patients. For example, the eGFR may underestimate the degree of renal impairment in cachectic or oedematous patients, resulting in excessive doses. While CrCl is preferred (as discussed earlier), another approach can be adopted. Providing height and weight are known, the *absolute GFR* (GFR_{ABS}) (see Box 1.9) can be calculated and used to determine dosage adjustments.

Box 1.9 Calculating absolute glomerular filtration rate and body surface area

$$GFR_{ABS} = eGFR \frac{BSA}{1.73}$$

$$BSA = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$

where GFR_{ABS} = absolute glomerular filtration rate; eGFR = estimated glomerular filtration rate; BSA = body surface area.

Drug interactions

Be alert to the fact that all drugs taken by patients, including over-the counter medicines, herbal products, and nutritional supplements, have the potential to cause clinically relevant drug interactions. The patient's diet can also affect drug disposition.

The pharmacological actions of a drug can be enhanced or diminished by other drugs, food, herbal products, and nutritional supplements. Clinically relevant and potentially significant drug–drug interactions are included in the monographs.

In terms of a drug–drug interaction, the actions of the *object* drug are altered by the *precipitant* in most cases. Occasionally, the actions of both object and precipitant can be affected.

While it is possible to predict the likelihood of a drug interaction, it is often difficult to predict the clinical relevance. Elderly patients or those with impaired renal and/or hepatic function are more at risk. Drug interactions may be overlooked and explained as poor compliance or even progressive disease. Knowledge of drug interaction processes can aid in the diagnosis of unexplained or unexpected response to drug therapy.

It is impossible to accurately determine the incidence of drug interactions. Knowledge of many drug–drug interactions comes from isolated case reports and/or small studies in healthy volunteers. It is, however, possible to indirectly assess a patient's risk; there are several factors that predispose patients receiving palliative care to a drug interaction (see Box 1.10).

Box 1.10 Factors that predispose a patient to drug interactions

- Advancing age
- Multiple medications
- Compromised renal/hepatic function
- More than one prescriber
- Comorbidity

While the majority of risks cannot be reduced, they can be anticipated and managed. For example, a thorough medication history should be taken upon presentation and must include over-the-counter medications and herbal or nutritional supplements. In some cases, changes to diet should be enquired about; for example, the effect of warfarin can be reduced by a diet suddenly rich in leafy green vegetables (a source of vitamin K).

As part of the multidisciplinary team, the pharmacist is an excellent source of information and is often involved in the recording of drug histories.

There are two main mechanisms involved in drug interactions:

- pharmacokinetic
- pharmacodynamic.

Pharmacokinetic

The precipitant drug alters the absorption, distribution, metabolism, or excretion of the object drug. Pharmacokinetic drug interactions are likely to be encountered in palliative care as many of the drugs used are substrates or inducers/inhibitors of cytochrome P450 isoenzymes (see ➔ *Metabolism* below). These interactions are often difficult to predict.

Absorption

CYP3A4, mainly found in the liver, is also present in the gut wall. It is involved in reducing the absorption of many drugs and is subject to both induction and inhibition (see ➔ *Metabolism* below). Grapefruit juice inhibits the action of CYP3A4 in the bowel (and liver with repeated consumption) and can lead to significant increases in bioavailability of several drugs, e.g. ciclosporin, diazepam, sertraline, simvastatin. This interaction is highly variable since the active component of the juice cannot be standardized. This interaction can occur even after consuming just 200mL of grapefruit juice and inhibition can persist for up to 72 hours. An interaction may occur, whatever the source, e.g. fresh grapefruit and grapefruit juices, including fresh, frozen, or diluted from concentrate. Drugs with a narrow therapeutic index are more likely to be affected.

The rate of absorption or amount of object drug absorbed can be altered by the precipitant. Delayed absorption is rarely of clinical relevance unless the effect of the object drug depends upon high peak plasma concentrations. If the amount of drug absorbed is affected, clinically relevant effects can occur.

Absorption interactions involving simple insoluble complex formation can be easily avoided by changing the administration time of the drugs involved, e.g. ciprofloxacin and antacids

Some interactions involve the induction or inhibition of P-gp, although the clinical significance of many such interactions remains unclear. Enhanced activity of P-gp will reduce the absorption and bioavailability of a drug. The effect of drugs and food on influx transporters is currently less well categorized but could well contribute to unexplained and unanticipated drug effects.

Distribution

Such interactions are usually of little clinical relevance and often involve alterations in protein binding.

The distribution of some drugs is dependent on the activity of P-gp, which also appears to act as a component of the blood–brain barrier; for example, P-gp can limit the entry of hydrophilic opioids into the brain. The clinical significance of induction or inhibition of P-gp is unclear.

Metabolism

Many drugs are metabolized via the hepatic cytochrome P450 system (see Box 1.3), which is subject to both inhibition and induction. CYP3A4 may account for the metabolism of up to 50% of currently used drugs; CYP2D6 may account for up to 25% (see ➔ *Cytochrome P450 tables* on the inside

back cover). The effect that smoking can have on drug therapy should not be overlooked (see Box 1.11).

Box 1.11 Smoking and potential drug interactions

- Tobacco smoke contains several polycyclic aromatic hydrocarbons (PAHs) that are potent inducers of CYP1A1, CYP1A2, CYP2B6, and, to a lesser extent, CYP2E1. PAHs can also induce glucuronide conjugation.
- Induction of CYP1A1 in the lungs causes activation of procarcinogens from tobacco smoke and is believed to be a major mechanism in the development of lung cancer.
- Although CYP1A1 is not important for drug metabolism, several drugs are substrates of CYP1A2 and CYP2B6 (see ➔ *Substrates* on the inside back cover). Metabolism of these drugs can be induced by tobacco smoke, potentially resulting in increased clearance of the drug and consequent clinically significant reductions in effects. Smokers may require higher doses of these drugs.
- Note that exposure to 'second-hand' smoke can produce similar effects.
- The PAHs cause these pharmacokinetic drug interactions, not nicotine. Thus, nicotine replacement therapy (NRT) will not cause these effects.
- The prescriber should consider a dosage reduction of drugs metabolized by CYP1A2 and CYP2B6 if a patient stops smoking. Similarly, doses of anxiolytics and hypnotics should be reviewed, unless NRT is initiated. If a patient starts smoking, doses of drugs metabolized by CYP1A2 and CYP2B6 may need increasing, whereas doses of anxiolytics and hypnotics may need reviewing.
- Tobacco smoke and NRT are both implicated in several pharmacodynamic drug interactions. Nicotine can have an alerting effect, thereby countering the action of other drugs.

Enzyme inhibition is the mechanism most often responsible for life-threatening interactions. It can also result in reduced drug effect where activation of a prodrug is required (for example, codeine has a reduced analgesic profile when administered with CYP2D6 inhibitors). Inhibition is generally caused by competitive binding for the isoenzyme between object and precipitant, although some may occur through irreversible inactivation of the isoenzyme (for example, a metabolite of clarithromycin binds irreversibly to CYP3A4, rendering it inactive). It follows that high doses of the precipitant will cause a greater degree of inhibition. Clinically relevant interactions can be evident within hours to short days. The effect of enzyme inhibition generally depends upon the half-life of the precipitating drug and the therapeutic index of the object drug. The effect will decrease as blood levels fall. Note that drugs competing for the same isoenzyme can give rise to competitive inhibition. The more drugs that are co-prescribed, the greater the risk of this occurring.

Induction can occur when the precipitant stimulates the synthesis of more isoenzyme, increasing metabolic capacity. It can take several days, or even weeks, to develop and may persist for a similar duration once the precipitant has been withdrawn. Problems with toxicity can occur if doses of the object drug are increased but are not reduced once the precipitant is stopped.

Many drugs are not metabolized by one specific pathway and for this reason, it is often difficult to precisely predict the outcome of a drug interaction. Nonetheless, although *in vivo* data may not be available for many drugs, *in vitro* evidence of metabolism and specific cytochrome P450 isoenzyme involvement can be used to anticipate and avoid a potentially dangerous drug interaction. The drug monographs in ➔ Chapter 3 mention actual and potential drug interactions.

Elimination

In palliative care, it is likely that the most common and potentially more clinically relevant elimination drug interactions will involve renal function. For example, with advancing age, renal function declines, but compensatory mechanisms are activated that involve the production of vasodilatory prostaglandins. NSAIDs can significantly impair this compensatory measure, such that there is marked reduction in renal function and consequential risk of drug interactions.

Pharmacodynamic

The pharmacological actions of the object drug are changed by the presence of the precipitant. Pharmacodynamic interactions can be additive or antagonistic in nature.

Additive

When two or more drugs with similar pharmacodynamic effects are coprescribed, the additive response may result in an exaggerated response or toxicity. Additive responses can occur with the main therapeutic action of the drug, as well as with the undesirable effects; for example, an SSRI plus tramadol may give rise to serotonin toxicity (ST) (see ➔ *Serotonin toxicity*, p. 29).

Antagonistic

When two drugs with opposing pharmacodynamic effects are coprescribed, there may be a net reduction in response to one or both drugs, e.g. warfarin and vitamin K, NSAIDs and angiotensin-converting enzyme inhibitors (ACE-Is), metoclopramide and cyclizine.

Serotonin toxicity

Serotonin, or 5-hydroxytryptamine (5-HT), has both central and peripheral actions mediated by seven distinct classes of 5-HT receptors (5-HT_1 to 5-HT_7), with a current total of 14 receptor subtypes (see Table 1.4). These receptors comprise GPCRs (5-HT_{1A-B}, 5-HT_{1D}, 5-ht_{1E}, 5-HT_{1F}, 5-HT_{2A-C}, 5-HT_4, 5-ht_{5A-B}, 5-HT_6, and 5-HT_7) and a ligand-gated ion channel (5-HT_3). Note that lower case (i.e. 5-ht) designates receptors that have not been established definitively in functional tests. Many polymorphisms and splice variants have been identified.

The raphe nuclei, located in the brainstem, are the primary location in the CNS for the production of serotonin. Serotonergic pathways that project from here to other areas of the brain are involved in modulating affective behaviour (depression and anxiety), appetite, attention, migraine, sexual behaviour, thermoregulation, and wakefulness. Pathways that project to the spinal cord are involved in nociception and motor tone. In the periphery, 5-HT functions as a local hormone. It is produced in enterochromaffin cells that line the GI tract and is involved in a multitude of processes, including bronchoconstriction, control of blood pressure through vasoconstriction or vasodilation (depending on the receptor), GI motility, and platelet aggregation. Serotonin has an important role in immunity and inflammation through complex interactions via numerous receptor subtypes located on, for example, platelets, mast cells, lymphocytes, neutrophils, and T-cells.

Table 1.4 Serotonin receptor families and subtypes

Receptor	Comments
5-HT_{1A}	The first serotonin receptor to be cloned. Close similarity to the β_1-adrenoceptor explains why some β_2 antagonists (e.g. pindolol, propranolol) have an affinity for some 5-HT_1 receptors. These receptors are located in pre- and post-synaptic regions. Activation of presynaptic autoreceptors at the somatodendritic end of the serotonin neurone in the raphe nuclei serves to inhibit serotonin release through a negative feedback mechanism. Post-synaptic heteroreceptors are also located in several areas of the brain, including the amygdala, hippocampus, hypothalamus, septum, and thalamus. 5-HT_{1A} agonism may have a positive effect in anxiety, depression, and reversal of memory impairment ('cognitive enhancers'), with the effect being dependent on whether pre- or post-synaptic receptor activity predominates. Interestingly, 5-HT_{1A} agonists have been shown to reverse opioid-induced respiratory depression. 5-HT_{1A} partial agonists diminish the EPS caused by undesirable dorsal striatal D_2 receptor blockade of both typical and second-generation antipsychotic drugs. Additionally, the 5-HT_{1A} receptor may have an analgesic role in several pain states, including neuropathic, inflammatory, and visceral pain; it is also involved in the descending pain pathway. This receptor is implicated in the development of ST

(*Continued*)

Table 1.4 (*Contd.*)

Receptor	Comments
5-HT_{1B}	This receptor is located in pre- and post-synaptic regions and functions in a similar manner to the 5-HT_{1A} receptor. 5-HT_{1B} receptors in the CNS serve as autoreceptors on axon terminals and may have a major detrimental role in antidepressant response. In addition, 5-HT_{1B} receptors are found on cerebral arteries and other vascular tissues where activation mediates contraction (and thus vasoconstriction). The 5-HT_{1B} receptor is involved in nociception, particularly migraine, where agonists serve to reduce inflammatory mediators and/or neurotransmission, as well as having a role in the descending inhibitory pain pathway. Ligands of 5-HT_{1B} receptors may also bind to 5-HT_{1D} receptors. Agonists of 5-HT_{1B} receptors (e.g. sumatriptan) have been developed for the treatment of migraine
5-HT_{1D}	Similar distribution and actions to the 5-HT_{1B} receptor, although at a reduced level
5-ht_{1E}	Although this receptor has been cloned, it has yet to be shown to have meaningful physiological functions *in vivo*
5-HT_{1F}	Distributed throughout the CNS where it acts as both an autoreceptor and a heteroreceptor. Like the 5-HT_{1B} receptor, it has a high affinity for triptans, but the relative contribution of either receptor to the efficacy of triptans in migraine is currently unknown
5-HT_{2A}	The 5-HT_{2A} receptor is widely distributed in peripheral tissues (e.g. platelets, cardiovascular and smooth muscle tissues), but also in the CNS (e.g. cortex, hippocampus), primarily on the post-synaptic membrane. In the periphery, it mediates contractile responses and regulates platelet aggregation. It may have a role to play in chronic kidney disease and insulin resistance. The 5-HT_{2A} receptor mediates the hallucinogenic effects of LSD. Clinically, there are currently no specific agonists or antagonists, but several drugs bind this receptor, in addition to others, e.g. trazodone, mirtazapine, olanzapine. Combined 5-HT_{2A} *inverse agonism* (e.g. olanzapine) and D_2 antagonism of second-generation antipsychotics may help to explain the reduced extrapyramidal effects displayed by such drugs. The role of the 5-HT_{2A} receptor in the descending pain pathway is unclear, as both facilitatory and inhibitory effects have been demonstrated. Implicated in the development of ST
5-HT_{2B}	Widely expressed in tissues such as gut, liver, and kidney, with only discrete distribution within the CNS. This receptor mediates smooth muscle contraction and may be implicated in pulmonary hypertension. 5-HT_{2B} agonism, whether direct or indirect, causes valvulopathic adverse effects, as illustrated by fenfluramine (withdrawn) and MDMA (ecstasy). It may also have a role to play in migraine, since the 5-HT_{2B} antagonists pizotifen and cyproheptadine are options for migraine prophylaxis. In the raphe nuclei, 5-HT_{2B} receptors may act as positive autoreceptors, opposing the actions of the 5-HT_{1A} and 5-HT_{1B} autoreceptors. 5-HT_{2B} autoreceptors may contribute to the effects of SSRI antidepressants. The 5-HT_{2B} receptor may have a facilitatory effect on pain transmission, such that antagonism may represent a novel approach to analgesia

Table 1.4 (*Contd.*)

Receptor	Comments
5-HT_{2C}	5-HT_{2C} receptors are invariably found within the CNS and located on post-synaptic membranes. They are involved in appetite control, food intake, mood, and possibly addiction and epilepsy. 5-HT_{2C} antagonism leads to weight gain and (together with H_1 antagonism) explains this effect displayed by certain drugs, including olanzapine and mirtazapine. In addition, antagonism has been shown to increase dopamine and noradrenaline levels in the prefrontal cortex and nucleus accumbens, which may produce an antidepressant action (drugs such as fluoxetine, mirtazapine, trazodone, and quetiapine are 5-HT_{2C} antagonists) or have a precognitive effect. 5-HT_{2C} agonists are being investigated as novel antipsychotics with reduced EPS since suppression of dopamine release appears to preferentially affect mesolimbic (e.g. nucleus accumbens) over nigrostriatal pathways. The role of the 5-HT_{2C} receptor in pain transmission is unclear, as both facilitatory and inhibitory effects have been demonstrated
5-HT_3	Unlike the other 5-HT receptors, the 5-HT_3 receptor is a ligand-gated ion channel and is located on the post-synaptic neurone. Several subunits have been cloned, although specific actions and implications have not been determined. 5-HT_3 receptors are found on neurones of both central and peripheral origin. Within the CNS, high densities of 5-HT_3 receptors are located within the area postrema and nucleus tractus solitarius. Antagonism using drugs such as ondansetron can successfully control nausea and vomiting, e.g. due to CINV or PONV. The 5-HT_3 receptor is also located in other areas of the human brain, including the hippocampus, amygdala, and caudate putamen, where it is believed to regulate the release of numerous neurotransmitters. It may prove to be a novel target for a range of conditions such as schizophrenia, depression, anxiety, and addiction. For example, it may contribute to the antidepressant activity of mirtazapine. This receptor also has an important facilitatory role in spinal cord transmission of pain. In the periphery, the 5-HT_3 receptor is localized to vagal afferents, enteric motor neurones, and intrinsic primary afferent nerves. 5-HT_3 receptor activation in the GI tract regulates motility and intestinal secretions. Finally, the 5-HT_3 receptor may have a role in central and systemic inflammation
5-HT_4	The 5-HT_4 receptor is widely expressed in the spinal cord, brain, cardiovascular tissues, and GI tract. In the CNS, it modulates acetylcholine release and may have a role in learning and memory. This receptor may also be implicated in the development of anxiety. In the GI tract, the 5-HT_4 receptor modulates motility through facilitating acetylcholine release and mediates intestinal secretions. The facilitatory or inhibitory role of the 5-HT_4 receptor in the descending pain system currently remains unclear
5-HT_{5A}	The 5-HT_{5A} receptor is located in superficial layers of the dorsal horn, lumbar dorsolateral nucleus, raphe nuclei, cerebral cortex, and hippocampus. It may have a role to play in psychiatric disorders (schizophrenia, bipolar disorder, anxiety, and depression), memory and cognition, obesity, and analgesia

(*Continued*)

Table 1.4 (*Contd.*)

Receptor	Comments
5-ht_{5B}	Although the receptor has been identified in humans, the gene is transcribed and translated into a non-functional protein
5-HT_6	The 5-HT_6 receptor is post-synaptic, located in the caudate putamen, nucleus accumbens, olfactory tubercle, and choroid plexus. It is believed to regulate the release of acetylcholine and have a role to play in cognition. The receptor has also been implicated in weight loss and anti-nociception. Many antidepressants and antipsychotics are antagonists, but the role this property has on their activity is unclear
5-HT_7	The 5-HT_7 receptor is post-synaptic and believed to regulate the release of serotonin; when blocked, serotonin release is disinhibited. It is expressed in vascular and non-vascular smooth muscle and the dorsal horn, hippocampus, thalamus, and hypothalamus. The receptor is believed to be involved in thermoregulation, circadian rhythms, memory, sleep, analgesia, and psychiatric disorders (e.g. depression, schizophrenia). 5-HT_7 agonists may have a significant analgesic effect at the spinal level, possibly through activation of GABAergic inhibitory interneurons. Several antidepressants (e.g. imipramine) and antipsychotics (e.g. clozapine, risperidone) act as moderate antagonists of the 5-HT_7 receptor, but a specific role in depression/schizophrenia has not been conclusively shown

EPS, extrapyramidal symptoms; ST, serotonin toxicity; CNS, central nervous system; CINV, chemotherapy-induced nausea and vomiting; PONV, post-operative nausea and vomiting; GI, gastrointestinal.

Source: data from Hoyer D, Serotonin receptors nomenclature. In: Tricklebank MD, Daly E, [eds], *The Serotonin System*, pp. 63–93, Copyright (2019), Elsevier; *Neural Plast.*, **2019**(4), Tao ZY, Wang PX, Wei SQ, *et al.*, The Role of Descending Pain Modulation in Chronic Primary Pain: Potential Application of Drugs Targeting Serotonergic System, pp. 1–16, Copyright (2019), Hindawi.

Several of the physiological actions of serotonin have been targeted with the development of antipsychotics, antidepressants, antiemetics, and triptans. These serotonergic drugs, however, do have unexpected or unwanted effects because of the widespread actions of serotonin. For example, SSRIs inhibit SERT which is responsible for their antidepressant actions. However, SERT is involved in transporting 5-HT into platelets (they cannot synthesize serotonin), which is needed during haemostasis. Consequently, SSRIs can lead to a reduction in platelet aggregation, thereby leading to an increase in bleeding time.

As the effects on serotonergic systems increase, whether by combining drugs with similar actions or by simple dose increases, what may appear as mild adverse effects can insidiously develop into a serious condition associated with increased serotonergic activity in both the periphery and CNS. ST, or serotonin syndrome (SS) as it is sometimes referred as, is a rare, but potentially life-threatening, condition associated with increased serotonergic activity. Iatrogenic increases in intrasynaptic serotonin concentrations can occur as a result of co-administration of drugs that have the net effect of increasing serotonergic neurotransmission. It may rarely occur

after initiation of a single serotonergic drug or by simply increasing the dose of a serotonergic drug. Specifically, stimulation of 5-HT_{1A} and 5-HT_{2A} receptors has been implicated as the root cause of ST, but no single receptor is likely to be solely responsible. In addition, it is thought that 5-HT_{2A} *antagonism* may also have a role (possibly shunting elevated levels of serotonin to any co-localized 5-HT_{1A} receptors), given the association between ST and second-generation antipsychotics (e.g. quetiapine). ST may also involve other neurotransmitter systems; for example, N-methyl-D-aspartate (NMDA) antagonism may play an important role in glutamate modulation of serotonergic function at post-synaptic 5-HT_{2A} receptors.

The list of drugs that have been implicated in ST is extensive. Drugs typically associated with ST include monoamine oxidase inhibitors (MAOIs) (monoamine oxidase A (MAO-A) plays a larger role in the breakdown of serotonin), SSRIs and serotonin–noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and trazodone. Other drugs that have been reported to cause ST include:

- opioids (dextromethorphan, methadone, tramadol, and tapentadol—inhibit SERT; fentanyl—5-HT_{1A} agonist)
- herbals (e.g. St John's wort—inhibits SERT and weak MAOI)
- drugs associated with abuse (e.g. cocaine, fenfluramine, 3,4-methylenedioxy methamphetamine ('ecstasy') (MDMA)).

The association of drugs (e.g. mirtazapine, metoclopramide, ondansetron) that block, rather than activate, 5-HT_{1A} or 5-HT_{2A} (although 5-HT_{2A} antagonism has been suggested as a possible cause), or do not directly increase synaptic serotonin concentrations, remains controversial.

Drug-induced ST may occur via several different mechanisms:

- increasing serotonin synthesis (e.g. dietary supplements such as L-tryptophan)
- increasing presynaptic release (e.g. levodopa, mirtazapine, MDMA)
- inhibition of serotonin reuptake (e.g. SSRIs, SNRIs, TCAs, dextromethorphan, trazodone, tramadol, methadone, MDMA, St John's wort, chlorphenamine)
- inhibition of serotonin metabolism (e.g. MAOIs, including linezolid and selegiline)
- activation of 5-HT_{1A} receptors (e.g. buspirone, fentanyl, trazodone)
- CYP450 inhibition (e.g. CYP2D6 inhibition by paroxetine and co-administration of tramadol; CYP3A4 inhibition by clarithromycin and co-administration with venlafaxine; CYP2C19 inhibition by fluconazole and co-administration with citalopram).

ST is characterized by a triad of mental (e.g. agitation, anxiety, delirium, restlessness, confusion, disorientation, excitement), autonomic (e.g. hyperthermia, tachycardia, tremor, diaphoresis, mydriasis, flushing), and neuromuscular disorders (e.g. clonus, hyperreflexia, myoclonus, rigidity), with a sudden onset of <24 hours after the beginning of treatment (serotonergic agent or CYP inhibitor) or dose change. Diagnosis is complex, but use of the Hunter Toxicity Criteria Decision Rules can be used as an aid:

- In addition to taking a serotonergic drug, the patient should meet *ONE* of the following conditions:
  - spontaneous clonus

- inducible clonus *AND* agitation or diaphoresis
- ocular clonus *AND* agitation or diaphoresis
- tremor *AND* hyperreflexia
- hypertonia *AND* temperature above 38°C *AND* ocular clonus or inducible clonus.

Treatment is largely symptomatic and includes discontinuation of the serotonergic agents; most patients improve completely within 24 hours upon withdrawal. Benzodiazepines may be used for anxiety and although effectiveness has not been thoroughly investigated, cyproheptadine may be useful (antagonist at several receptors, including 5-HT_{1A} and 5-HT_{2A}).

References and further reading

1. Raehal KM, Walker JK, Bohn LM. Morphine side effects in beta-arrestin 2 knockout mice. J Pharmacol Exp Ther. 2005;**314**:1195–201.
2. Gillis A, Gondin AB, Kliewer A, *et al*. Low intrinsic efficacy for G protein activation can explain the improved side effect profiles of new opioid agonists. Sci Signal. 2020;**13**:eaaz3140.

Hoyer D. Serotonin receptors nomenclature. In: Tricklebank MD, Daly E (eds). *The Serotonin System*. London: Elsevier; 2019. pp. 63–93.

Tao ZY, Wang PX, Wei SQ, Traub RJ, Li JF, Cao DY. The role of descending pain modulation in chronic primary pain: potential application of drugs targeting serotonergic system. *Neural Plast*. 2019;**2019**:1389296.

Chapter 2

Prescribing guidance

Unlicensed use of medicines

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) grants a marketing authorization (previously referred to as product licence) to pharmaceutical companies enabling them to market and supply a product for the specific indication(s) stated in the summary of product characteristics (SmPC). For a period of 2 years following 1 January 2021, the UK will continue to adopt decisions taken by the European Medicines Agency on the approval of new marketing authorizations.

Occasionally, there may be clinical situations when the use of unlicensed medicines (those without a marketing authorization) or use of licensed medicines outside the terms of the licence (e.g. outside defined indications, doses, or routes of administration, or contrary to listed warnings) may be judged by the prescriber to be in the best interest of the patient.

The following healthcare professionals can (currently) prescribe an unlicensed medicine, or a licensed medicine outside the terms of its marketing authorization (also described as 'off-label' use):

- doctors
- dentists
- independent nurse and pharmacist prescribers
- supplementary prescribers* (provided these are part of a patient's clinical management plan).

Although the use of unlicensed medicines in palliative care is rare (e.g. olanzapine injection for use by continuous subcutaneous infusion (CSCI) is imported into the UK), the off-label use of licensed medicines is both common and necessary.

The unlicensed use of medicines is highlighted in relevant monographs by the symbol ✢

The patient should be informed that an unlicensed medicine, or a licensed medicine outside the terms of its marketing authorization, is to be used; consent should be documented in the patient's case notes. Although some may feel this is impractical, given the widespread use in palliative care, certain inpatient units gain global consent during the admission process.

* Chiropodists/podiatrists, community nurses, midwives, nurses, optometrists, pharmacists, physiotherapists, or radiographers.

Legal categories of medicines

Medicines for human use are classified in the following way. There are three classes of medicine, as defined by the Medicines Act 1968:

- *general sales list (GSL)*: a medicinal product that can be sold or supplied without the supervision of a pharmacist
- *pharmacy medicine (P)*: a medicinal product that is available for sale from a pharmacy under the supervision of a pharmacist
- *prescription-only medicine (POM)*: a medicinal product that can be sold or supplied from a pharmacy (or a dispensing doctor in specific circumstances) in accordance with a prescription from an appropriate practitioner.

The Misuse of Drugs Act 1971 (as amended) and subsequent Misuse of Drugs Regulations define the use of controlled drugs, which are classified into five schedules, according to different levels of control.

NB—as of 23 April 2012, for indications for which they are clinically competent, independent nurse and pharmacist prescribers can prescribe, administer, and give directions for the administration of all Schedule 2, 3, 4, and 5 controlled drugs. The only exceptions are diamorphine, dipipanone, and cocaine for the treatment of addiction.

- *Schedule 1 (CD1)*: production, possession, and supply of drugs in this Schedule are limited, in the public interest, to purposes of research or other special purposes; includes drugs such as cannabis, lysergic acid diethylamide (LSD), and ecstasy-type substances, which have virtually no therapeutic use.
- *Schedule 2 (CD2)*: includes amphetamine (e.g. methylphenidate), ketamine, opioids (e.g. alfentanil, diamorphine, fentanyl, methadone, morphine), and tapentadol. Note that parenteral codeine and dihydrocodeine are classified as Schedule 2 drugs. These drugs are subject to prescription requirements (see Box 2.1), safe custody (i.e. CD cupboard), and the need for drug registers.
- *Schedule 3 (CD3)*: includes barbiturates, buprenorphine, gabapentin, midazolam, pregabalin, temazepam, and tramadol. There is no requirement for drug registers. Except for temazepam, these drugs are subject to prescription requirements (see Box 2.1). Safe custody requirements *do* apply to Schedule 3 controlled drugs (e.g. temazepam, buprenorphine, flunitrazepam, diethylpropion), but there are notable exceptions (e.g. gabapentin, midazolam, phenobarbital, pregabalin, tramadol). Note that some centres may insist upon entries into controlled drugs registers and/or safe storage for certain Schedule 3 drugs.
- *Schedule 4 Part 1 (CD4a)*: includes benzodiazepines (except midazolam and temazepam), zopiclone, and zolpidem. These drugs are not subject to controlled drugs prescription or safe storage requirements and there is no need for a register.

- *Schedule 4 Part 2 (CD4b)*: includes androgenic and anabolic steroids. These drugs are not subject to controlled drugs prescription or safe storage requirements and there is no need for a register.
- *Schedule 5 (CD5)*: includes certain controlled drugs, e.g. codeine, cophenotrope, pholcodine, and morphine, which are exempt from full control when present in medicinal products of low strength.

The quantity of Schedule 2, 3, or 4 controlled drugs to be prescribed at any one time should not exceed 30 days' supply. This represents good practice, rather than a legal requirement, as there may be circumstances where there is a genuine need to prescribe >30 days' supply. Note, however, that prescriptions for Schedule 2, 3, or 4 controlled drugs are only valid for 28 days.

Box 2.1 Prescription requirements for Schedule 2 and 3 controlled drugs

Prescriptions for controlled drugs must be indelible, signed by the prescriber, and dated, and specify the prescriber's address. Where the Electronic Prescribing Service exists, advanced electronic signatures can be accepted for Schedules 2 and 3 controlled drugs.

The prescription must always state:

- the name and address of the patient (a PO box is not acceptable)
- in the case of a preparation, the form and, where appropriate, the strength of the preparation
- either the total quantity (in both words and figures) of the preparation or the number (in both words and figures) of dosage units to be supplied; in any other case, the total quantity (in both words and figures) of the controlled drug to be supplied
- the dose
- the words 'for dental treatment only' if issued by a dentist.

Travelling abroad with medicines

When planning to travel abroad, patients need to be aware of the laws that govern medicine use in both the UK and their destination(s). It is the patient's responsibility to take the necessary steps to ensure compliance with these laws. Note that certain over-the-counter (OTC) medicines in the UK may be controlled drugs in other countries.

If *any* medicines are to be taken abroad (including OTC medicines, e.g. co-codamol 8/500, pseudoephedrine 60mg), the patient should contact the embassy, consulate, or high commission of the country or countries to be visited regarding local policies on the import of medicines (see Box 2.2).

UK requirements for export/import depend upon the medicines in question and the duration of travel abroad:

Less than 3 months

- For all prescribed medicines, patients are advised to carry a letter from the prescribing doctor that states the:
  - patient's name, address, and date of birth
  - outbound and inbound dates of travel
  - destination(s)
  - name, form, dose, and total amount of medicine(s) being carried.
- Certain countries may require additional information (e.g. particulars of the illness). Details of the information can be obtained from the embassy, consulate, or high commission.

More than 3 months

- Patients carrying any amount of medicines listed in Schedules 2, 3, or 4 (Part 1) of the Misuse of Drugs Regulations 2001 will require a personal export/import licence. The application form can be downloaded from the Home Office website (see Box 2.2).
- The application must be supported by a covering letter from the prescriber, which should state the:
  - patient's name and address
  - quantity of medicine(s) to be carried
  - name, strength, and form of medicine(s) to be carried
  - destination(s)
  - outbound and inbound dates of travel.
- The completed form, together with the covering letter, should be sent to the Home Office (see Box 2.2).
- Alternatively, the completed form, together with a scanned copy of the covering letter, may be emailed to the Home Office (see Box 2.2).
- The patient must be advised that application for a personal licence can take at least 2 weeks.
- Patients taking other POMs abroad are advised to carry a letter from the prescribing doctor that states the:
  - patient's name, address, and date of birth
  - outbound and inbound dates of travel
  - destination(s)
  - name, form, dose, and total amount of medicine(s) being carried.
- Certain countries may require additional information (e.g. particulars of the illness). Details of the information can be obtained from the embassy, consulate, or high commission.

Box 2.2 Useful contact details

Embassy, consulate, and high commission

https://www.gov.uk/government/publications/foreign-embassies-in-the-uk

Application form for personal licence

https://www.gov.uk/government/publications/personal-import-export-licence-application-form

Home Office

Home Office, Drugs & Firearms Licensing Unit
Fry Building
2 Marsham Street
London
SW1P 4DF
Email: dflu.ie@homeoffice.gov.uk
Tel.: (020) 7035 6330 (in case of emergency)

When travelling by air, POMs should be carried:

- in the original packaging
- in hand luggage*
- with a valid personal licence (if applicable)
- with a covering letter from the prescriber (see above), unless a personal licence is held.

Patients using insulin are advised to check:

- the availability of insulin in the country they are visiting
- they have sufficient supplies of insulin
- the correct storage of insulin while travelling
- the timing of meals and insulin administration while travelling
- the possible effects of changing to different time zones
- plans for emergency situations, should they become unwell.

A useful website to refer to is: https://www.diabetes.org.uk/guide-to-diabetes/life-with-diabetes/travel.

* Due to liquid restrictions, airport and airline regulations must be checked prior to departure. As of June 2008, in the UK, medicines essential for the journey may be permitted in quantities of >100mL. The patient *must* have secured prior agreement of the airline and airport, in addition to having the documentation described above.

Drugs and driving

Section 4 of the Road Traffic Act 1988 states that it is an offence to drive, attempt to drive, or be in charge of a vehicle when unfit through taking drugs. Section 5A of the Road Traffic Act 1988, as amended in April 2013, adds an additional offence of driving with certain specified drugs in excess of specified levels (see Table 2.1). This came into force in England and Wales in March 2015 (for Scotland, refer to https://www.mygov.scot/illegal-drugs-driving-scotland/). This new legislation also provides for a statutory 'medical defence' for patients taking their medicines as prescribed or in accordance with product information. Note, however, that if a patient's driving were impaired due to drugs, Section 4 of the Road Traffic Act 1988 does not distinguish between illegal drugs and prescribed medication, and statutory 'medical defence' would not apply.

It remains the responsibility of all drivers to consider whether their driving is, or could be, impaired by their medicines. Patients should be advised that impairment might be present even in the absence of subjective symptoms.

Some prescription drugs and OTC medicines can impair skills needed for safe driving. Examples of such effects include blurred vision, dizziness, drowsiness, hypotension, and impaired judgement. In many cases, these effects are dose-dependent and may diminish with time. In general, any drug with a prominent central nervous system (CNS) effect has the potential to impair an individual's ability to operate a vehicle. The Driver and Vehicle Licensing Agency (DVLA) recommends that healthcare professionals prescribing or dispensing medication should consider the risks associated with each drug, or combination of drugs, and take the opportunity to appropriately advise their patients.

Patients should generally be warned to avoid driving after commencing, or when titrating, potentially sedating medication. Driving should not be attempted unless the patient feels safe to do so and any adverse effects of the drug(s) have diminished. This may take up to a week after commencing or increasing doses of certain drugs (e.g. opioids). If a patient uses rescue

Table 2.1 Drugs specified by Section 5A of the Road Traffic Act 1988

Group A ('illegal' drugs—zero tolerance)	Group B (licensed drugs)
Cannabis	Amphetamine
Cocaine	Clonazepam
Diamorphine (heroin)	Diazepam
Ketamine	Flunitrazepam
Lysergic acid diethylamide (LSD)	Lorazepam
MDMA (ecstasy)	Methadone
Methamphetamine	Morphine
	Oxazepam
	Temazepam

doses of opioids to treat pain flares (whether due to breakthrough cancer pain or poorly controlled background pain), driving should be avoided for up to 3 hours or until after any effect that could impair driving subsides. Patients should also be warned that cognitive effects will be exacerbated by concurrent use of alcohol or other medication, whether prescribed, bought OTC, or illicit.

When considering the prescription of new drugs, the patient's existing treatment should be reviewed. Drug interactions may affect drug metabolism and excretion or could produce additive or synergistic interactions. Refer to drug monographs in ➔ Chapter 3 for relevant prescribing information, including possible effects on driving and potential drug interactions. A selection of drugs that may cause problems is described below.

Anticholinergic drugs

- Examples include amitriptyline, cyclizine, glycopyrronium, hyoscine (butyl- and hydrobromide), levomepromazine, nortriptyline, olanzapine, oxybutynin, paroxetine, and propantheline.
- Anticholinergic effects that can impair driving performance include ataxia, blurred vision, confusion, and sedation.

Antidepressants

- Examples include amitriptyline, citalopram, fluoxetine, mirtazapine, nortriptyline, paroxetine, trazodone, and venlafaxine.
- In general, antidepressants that have antihistamine, anticholinergic, or α-adrenergic properties are likely to be problematic. While the adverse effects of SSRIs tend to be mild and well tolerated, patients should be made aware of potential problems that may impair driving such as sleep disturbances (e.g. insomnia leading to daytime drowsiness), anxiety, and restlessness.

Antiemetics

- Many drugs from different classes are used as antiemetics, e.g. 5-HT_3 antagonists, anticholinergics, antihistamines, antipsychotics, and dopamine antagonists.
- Adverse effects that may impair driving performance include blurred vision, confusion, dystonias, headache, and sedation.

Anti-epileptic drugs

- Examples include carbamazepine, clonazepam, levetiracetam, and sodium valproate.
- In the UK, patients with epilepsy can drive (cars and motorcycles) when they have been seizure-free for 6–12 months, dependent upon the seizure type.
- In the case of epilepsy, when treatment is being withdrawn, patients should not drive during the withdrawal period and for 6 months after completion.
- When prescribed for indications other than epilepsy, patients should not drive during treatment initiation, withdrawal, or dosage titration due to the risk of potential adverse effects that may impair driving performance.

Antihistamines

- First-generation antihistamines (e.g. chlorphenamine, cyclizine, cyproheptadine, promethazine) may have pronounced CNS effects and have been shown to impair driving performance. Of concern, patients may experience impairment even in the absence of subjective symptoms. Patients who take sedating antihistamines should be advised not to drive.
- In contrast, most non-sedating antihistamines (e.g. cetirizine, loratadine) cause less sedation and therefore lower the risk of driving impairment when used at recommended doses.

Antipsychotics

- Both typical and atypical antipsychotic medications have a strong potential to impair driving performance through various CNS effects. Some of the older generation of antipsychotics are sedating, and all produce extrapyramidal symptoms (EPS). Although atypical drugs have a lower tendency to cause EPS, many are also sedating. An additional problem with antipsychotics is the risk of hypotension which may cause light-headedness or fatigue, further impairing driving performance.

Anxiolytics/benzodiazepines

- Benzodiazepines impair driving and increase the risk of road traffic accidents. At low doses, they cause sedation, while at higher doses, the effects are comparable to those of alcohol intoxication.

Diabetic treatment

- Requirements differ, depending on the licence held (i.e. car, motorbike, lorry, bus, or coach) and the medication prescribed.
- Note that it is a legal requirement for drivers with insulin-treated diabetes to monitor glucose levels at times relevant to driving (no more than 2 hours before the start of a journey, and every 2 hours throughout the journey; no more than 2 hours should pass between the pre-driving glucose check and the first glucose check after driving has commenced).
- For further information, refer to https://www.gov.uk/diabetes-driving.

Opioid analgesics

- Opioid analgesics do not seem to adversely affect the driving performance of patients with cancer who have been on long-term stable doses.
- Following dose adjustments, performance may be affected for about 7 days. If rescue doses are used, the patient should be advised not to drive for at least 3 hours afterwards or until after any effect that could impair driving subsides.

Managing pain

Definitions

The International Association for the Study of Pain (IASP) revised the definition of pain in 2020 and included six key notes:[1]

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage:

- *pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors*
- *pain and nociception are different phenomena (pain cannot be inferred solely from activity in sensory neurons)*
- *through their life experiences, individuals learn the concept of pain*
- *a person's report of an experience as pain should be respected*
- *although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being*
- *verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain*

Pain is usually classified in temporal terms as either acute or chronic, depending on the onset and duration of pain. *Acute pain* is typically of short duration, which is arbitrarily taken to be <3 months. It serves as a warning for injury or the potential for further harm, responds well to analgesia, and subsides as healing occurs. *Chronic pain* serves no purpose and generally does not relate to injury (except cancer pain), persisting beyond the usual healing period. Response to analgesia can be unpredictable.

Pain can be further divided into three types, as defined by IASP, based on aetiology and clinical features. A fourth unofficial classification describes the proportion of patients who present with an overlap of symptoms of all three.

- *Nociceptive pain* is caused by stimulation of nociceptors in the peripheral nervous system and is produced by thermal, chemical, or mechanical damage. This includes pain caused by inflammation.
  - *Somatic pain* is often described as aching or throbbing and is generally localized and constant; it can be precipitated by movement and usually responds well to classic analgesics.
  - *Visceral pain* is described as a constant, sharp pain (e.g. bowel colic). It is often diffuse and poorly localized, and the pain may be referred to other non-visceral areas (e.g. shoulder tip pain from the gall bladder). Visceral pain usually responds well to classic analgesics, although occasionally adjuvant analgesics are required, e.g. bowel colic (hyoscine butylbromide).
- *Neuropathic pain* is caused by damage to, or changes in, the somatosensory nervous system (e.g. tumour infiltration, nerve compression, chemotherapy) and can occur spontaneously in the absence of a stimulus. In essence, it is caused by dysfunctional plasticity that alters nociceptive pain transmission, leading to enhanced responses to both noxious and innocuous stimuli. Depending on the nerve affected, the pain may be described as shooting, stabbing, lancinating,

electric, burning, cold, or itching. Neuropathic pain typically responds poorly to common analgesics; adjuvant analgesics are generally required. The patient may display signs of allodynia (abnormal pain response to non-painful stimulus) or hyperalgesia (heightened response to painful stimulus).

- *Nociplastic pain* is defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. Conditions that may be described as nociplastic pain include irritable bowel syndrome, fibromyalgia, and headaches.
- *Mixed pain* is an overlap of nociceptive, neuropathic, and nociplastic pain mechanisms. It is the category into which cancer pain falls. Tumour growth can induce tissue damage and the release of inflammatory mediators, as well as causing direct nerve damage through compression or infiltration. Note that cancer patients may also experience neuropathic pain due to chemotherapy or comorbidities such as diabetes mellitus. Patients with mixed pain typically have other comorbidities, such as depression, anxiety, and sleep disorder, which can negatively impact on response to treatment.

The pain experience is a complex process that involves signalling systems and modulation from higher centres of the brain (facilitation or inhibition), leading to a unique perception. It is a subjective experience that can be influenced by many factors, including emotional state, past experiences, attention, and distraction, which can serve to either augment or attenuate the pain experience. Dame Cicely Saunders introduced the concept of *total pain* to describe the suffering that encompasses a person's physical, psychological, social, spiritual, and practical struggles. *Physical pain* may be caused by the illness itself or by treatment related to the illness (e.g. chemotherapy). *Psychological pain* can be caused by feelings of helplessness or hopelessness, which is associated with anxiety or depression. *Social pain* is associated with the threat of impending separation or loss, e.g. realization that the patient will not be able to see a young child grow up. *Spiritual pain* is experienced when the situation does not fit with the person's understanding of the meaning of life.

Mechanisms

Nociceptors are involved in the transduction of tissue damage into an electric signal that can be transmitted from the periphery to the CNS. They are the free nerve endings of primary afferent pain fibres: myelinated Aδ fibres and unmyelinated type C fibres which synapse with second-order neurones in the dorsal horn of the spinal cord (except those in the head or face). These release excitatory neurotransmitters, including glutamate, substance P, and calcitonin gene-related peptide (CGRP). Various inflammatory mediators may bathe nociceptors, such as hydrogen ions, bradykinin, and prostaglandins, which can sensitize nociceptors and make them more prone to activating at lower stimulation thresholds (consider the effects of sunburn and increased sensitivity to heat). The ascending sensory pathways

transmit the noxious stimuli received by dorsal horn neurones to various regions of the brain. Areas such as the primary and secondary somatosensory cortices, anterior cingulate cortex (ACC), prefrontal cortex (PFC), amygdala, thalamus, cerebellum, and periaqueductal grey (PAG) have been identified as regions associated with the perception of pain. Sensory aspects of pain are established by activity in cortical areas through relays in the thalamus, whereas memory and affective components of pain are established by spinoreticular and spinomesencephalic tracts projecting to the limbic areas of the brain such as the amygdala, hypothalamus, PAG, and nucleus accumbens (NAc). Persistent inputs into the limbic areas may contribute to the comorbidities that patients with cancer pain often report such as anxiety, depression, and insomnia. Pain is thus a *sensory and emotional experience* which is always subjective and is influenced by factors such as cognition (e.g. distraction), emotional state, and beliefs.

In addition to the ascending sensory pathways, higher centres of the brain, such as the PAG and rostral ventromedial medulla (RVM), project to the spinal cord, forming both descending modulatory facilitatory and inhibitory pathways. These monoaminergic pathways utilize the neurotransmitters noradrenaline and serotonin. The descending noradrenergic pathway has only anti-nociceptive effects; the serotonergic pathway, in contrast, has been shown to exert both anti-nociceptive and nociceptive effects. The PAG receives inputs from the amygdala and spinal dorsal horn, and forms part of the endogenous pain inhibitory system primarily through its reciprocal connections with the RVM. The RVM is thought to be the final common relay in descending modulation of pain, projecting to the spinal dorsal horns and having both inhibitory and facilitatory effects. Due to the connection to the limbic system, emotional state can impact on these inhibitory and facilitatory descending pathways. Interestingly, chronic pain is considered to be caused by an imbalance between these inhibitory and facilitatory descending pain pathways. Changes in the limbic areas of the brain are precipitated by persistent inputs that cause common comorbidities such as anxiety and depression. Thus, these comorbidities can impact on the pain experience, leading to a situation of negative reinforcement.

Pain assessment

Cancer pain is complex and will generally have multiple causes. Aside from pain that arises as a direct consequence of the cancer, patients may also experience other pains that are precipitated by treatment such as chemotherapy (i.e. chemotherapy-induced peripheral neuropathy (CIPN)), radiotherapy, surgery, or drugs. For example, opioids can cause painful constipation and bortezomib may cause peripheral neuropathy. Underlying emotional issues, such as anxiety, depression, insomnia, fear, or anger, can have a direct impact on a patient's pain experience. Addressing these issues, in addition to administering analgesia, can help to reduce the patient's pain experience. Successful pain management will involve a multidisciplinary approach that also considers the psychological, social, and spiritual needs, i.e. addresses total pain. Drug therapy alone is unlikely to be adequate

treatment for chronic pain of any cause. Successful pharmacological treatment of cancer pain relies on an accurate pain assessment, with an appreciation of the underlying pathophysiology. A key component of a successful management plan involves regular reassessment to determine:

- the efficacy of treatment
- the tolerability of treatment and management of any emergent adverse effects
- any change in response (the need to increase doses of opioids does not always indicate disease progression; tolerance or opioid-induced hyperalgesia (OIH) may have developed)
- whether the treatment is ineffective or inappropriate.

Treatment of pain

A comprehensive strategy for the treatment of cancer pain should include both pharmacological and non-pharmacological approaches. While non-pharmacological measures (e.g. cognitive behavioural therapy, stress management, acupuncture) have an important role, medication forms a critical aspect of care.

In 1986, the World Health Organization (WHO) proposed a pain ladder as a stepwise approach to analgesia for cancer pain. The WHO subsequently reviewed this approach and introduced new guidelines for management of cancer pain in 2018. These new guidelines state that administration of analgesics should be given 'by mouth', 'by the clock', 'for the individual', and with 'attention to detail'. This is similar to the older guidelines, but with emphasis now on individual pain management. The need for 'attention to detail' states that the patient (or carer) should be given written information about the medication prescribed, including information about potential adverse effects. Table 2.2 summarizes the latest WHO approach to cancer pain relief.

The WHO describes the widespread use of the analgesic ladder for pain management but acknowledges it is only a general guide to pain management. It is accepted today that the analgesic ladder should be considered a framework, rather than a rigid protocol, and the severity or type of pain should determine the analgesic(s) to be used.

Significant progress has been made in recent years in the understanding of pain mechanisms and analgesic pharmacology. While the WHO analgesic ladder remains a useful educational tool, it is now recognized that a more individualized model of managing cancer pain is needed, one that adopts a mechanism-based and multimodal approach.

Table 2.2 WHO recommendations for pharmacological and radiotherapeutic management of cancer pain

Initiation of pain relief

- To achieve rapid, effective, and safe pain control, NSAIDs, paracetamol, and opioids should be used at initiation of pain management, either alone or in combination, depending on clinical assessment.
- Patients with mild to moderate pain should not be prescribed NSAIDs or paracetamol alone; in such circumstances, co-prescription with a low dose of an oral opioid is recommended.

Maintenance of pain relief

1. *Which is the most effective opioid for maintaining pain relief?*

Any opioid may be considered for maintenance of pain relief (note that NICE Clinical Guideline [CG140] recommends oral morphine). The choice is made on an individual basis and guided by pharmacokinetics, contraindications, and adverse effects.

2. *Which is the most effective opioid for treating breakthrough pain?*

Refer to *Opioid-induced hyperalgesia and tolerance*, p. 51.

The WHO recommends breakthrough pain should always be relieved with rescue opioid medication, based on clinical experience and patient need. The guideline specifically recommends standard-release oral morphine, despite its pharmacokinetic profile not matching the temporal profile of most breakthrough pain. The cost of certain formulations, such as transmucosal fentanyl, precluded their inclusion.

3. *What is the evidence for the practice of opioid rotation or opioid switching, as compared to continuing use of one opioid?*

Refer to *Breakthrough cancer pain*, p. 54.

The WHO makes no recommendation for or against the practice of opioid switching or rotation because of the lack of evidence.

4. *What is the evidence for the benefit of administering modified-release morphine regularly, as compared to standard-release morphine on a 4-hourly or an 'as required' basis?*

There is moderate strength of evidence of no difference in pain relief between modified-release and standard-release morphine. Regular doses of standard-release oral morphine or regular doses of modified-release morphine should be used to maintain effective and safe pain relief. With either formulation, standard-release oral morphine should be used as rescue medicine.

5. *Is there benefit for using the subcutaneous, transdermal, or transmucosal routes, as compared to the intramuscular and intravenous routes, when the oral route for opioids is inappropriate?*

Oral administration of opioids is usually preferable, whenever possible, to avoid the discomfort, inconvenience, and expense of parenteral administration. When oral or transdermal routes are not possible, the subcutaneous route is preferred due to safety and reduced infection risk and convenience (intravenous) and risk of pain and injury at injection site (intramuscular).

Table 2.2 *(Contd.)*

Adjuvant medicines for cancer pain management
1. *Steroids*
Adjuvant steroids should be given to achieve pain control when indicated. They are commonly used in management of metastatic bone pain, neuropathic pain, and visceral pain. A steroid with the least mineralocorticoid effect (e.g. dexamethasone) is preferable if the underlying condition is complicated, in part, by peritumoural oedema.
2. *Antidepressants/anticonvulsants*
Despite being commonly used to manage cancer-related neuropathic pain, the WHO makes no recommendation for or against the use of antidepressants and/or anticonvulsants to treat cancer-related neuropathic pain.
Pain related to bone metastases
1. *Bisphosphonates/monoclonal antibodies*
A bisphosphonate should be used to prevent and treat bone pain. The WHO makes no recommendation for or against the use of monoclonal antibodies to prevent and treat bone pain.
2. *Radiotherapy*
Single-dose fractionated radiotherapy should be used when radiotherapy is indicated and available.
3. *Radioisotopes*
The WHO makes no recommendation for or against the use of radioisotopes to treat bone pain.

Source: data from World Health Organization (WHO), *WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents*, Copyright (2018), World Health Organization. Available at https://www.who.int/publications/i/item/9789241550390.

NSAID, non-steroidal anti-inflammatory drug; WHO, World Health Organization.

Reference and further reading

1. Raja SN, Carr DB, Cohen M, *et al*. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020;**161**(9):1976–82.
Clark D. 'Total pain', disciplinary power and the body in the work of Cicely Saunders, 1958–1967. *Soc Sci Med*. 1999;**49**:727–36.
Melzack R. Pain and the neuromatrix in the brain. *J Dent Educ*. 2001;65:1378–82.
National Institute for Health and Care Excellence. Palliative care for adults: strong opioids for pain relief. Clinical guideline [CG140]. 2012 (updated 3 August 2016). Available from: https://www.nice.org.uk/guidance/cg140. Accessed 22 February 2021.
Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. *Curr Opin Support Palliat Care*. 2014;**8**:143–51.
World Health Organization. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. 2019. Available from: https://www.who.int/publications/i/item/9789241550390. Accessed 10 July 2022.

Selection of an NSAID

- All non-steroidal anti-inflammatory drugs (NSAIDs) are associated with renal adverse effects, in addition to cardiovascular (CV) and/or gastrointestinal (GI) toxicity. Table 2.3 facilitates the selection of an appropriate systemic NSAID, based on CV and GI risk factors.

- Topical administration provides an alternative route that reduces the risks associated with systemic NSAIDs. Although topical NSAIDs are considered relatively safer, they do produce local effects and systemic adverse effects have been reported (e.g. acute renal impairment, asthma, dyspepsia, and GI bleeding). The safety of topical NSAIDs therefore remains unclear.
- NSAIDs produce their pharmacological effects by inhibiting the activity of cyclo-oxygenase (COX)-1 and/or COX-2 enzymes. They vary substantially in terms of clinical efficacy and safety, but the affinity for COX-2, relative to COX-1, is believed to lead to the observed differences in GI and CV risks. All NSAIDs affect renal function, irrespective of COX selectivity.
- NSAIDs are contraindicated for systemic use in severe hepatic impairment because of increased bioavailability and the high risk of precipitating GI bleeding and renal failure.
- Before prescribing an NSAID, consider whether alternative treatment would be appropriate (e.g. non-pharmacological, topical NSAID, paracetamol).
- Prescribe the lowest effective dose of NSAID for the shortest time necessary. Review response to treatment *after 14 days*. Discontinue if no improvement.
- Diclofenac, even in doses available OTC, elevates the risk of CV toxicity. Other NSAIDs should be considered.
- Celecoxib has a superior GI safety profile, compared with other NSAIDs, while proving to be non-inferior to naproxen or ibuprofen in terms of CV safety.
  - Even though COX-2 inhibitors are *contraindicated* for use in patients with established ischaemic heart disease and/or cerebrovascular disease and also in those with peripheral arterial disease, current data suggest celecoxib (at doses ≤200mg/day) is non-inferior to several

Table 2.3 Selection of NSAIDs according to cardiovascular and gastrointestinal risk factors

Step	No cardiovascular or gastrointestinal risk(s)	Cardiovascular risk(s) ± gastrointestinal risk(s)	Gastrointestinal risk(s) No cardiovascular risks(s)
1	Alternative analgesia	Alternative analgesia	Alternative analgesia
2	Non-selective NSAID* or celecoxib	Naproxen* or celecoxib[§*] (≤200mg/day)	Celecoxib[§*] (≤200mg/day) or ibuprofen

* With gastroprotection (e.g. proton pump inhibitor).

§ The summary of product characteristics (SmPC) currently contraindicates its use in patients with established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease; current data support its use in patients with cardiovascular disease.

traditional NSAIDs (e.g. ibuprofen, naproxen) which remain licensed for use in these conditions.
  - Higher doses of celecoxib will attenuate this CV benefit.
- In patients at risk of CV toxicity, blood pressure (BP) and renal function should be assessed prior to, and within, 7 days of starting an NSAID/COX-2 inhibitor or after increasing the dose.
- All patients receiving long-term treatment with an NSAID/COX-2 inhibitor should receive gastroprotective therapy, i.e. proton pump inhibitor (PPI), misoprostol, H_2 antagonist (usually reserved if a PPI is not possible). Use PPIs with caution in patients receiving clopidogrel, and ensure routine monitoring of urea and electrolytes (U&Es) (sodium in particular).

Further reading

Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. *Br J Anaesth*. 2019;**123**:e412–23.

Nissen SE, Yeomans ND, Solomon DH, *et al*. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;**375**:2519–29.

Solomon DH, Husni ME, Libby PA, *et al*. The risk of major NSAID toxicity with celecoxib, ibuprofen, or naproxen: a secondary analysis of the precision trial. *Am J Med*. 2017;**130**:1415–22.

Yeomans ND, Graham DY, Husni ME, *et al*. Randomised clinical trial: gastrointestinal events in arthritis patients treated with celecoxib, ibuprofen or naproxen in the PRECISION trial. *Aliment Pharmacol Ther*. 2018;**47**:1453–63.

Opioid-induced hyperalgesia and tolerance

Opioid analgesics were originally used for the short-term management of acute pain. It is accepted practice to see the long-term use of these drugs for cancer pain. Consequently, unfamiliar and unexpected adverse effects may develop such as analgesic tolerance and hyperalgesia. Both conditions are often overlooked as potential complications of opioid therapy.

Analgesic tolerance refers to a progressive lack of response to a given dose of opioid upon chronic administration and, in the case of cancer pain, not readily attributable to advancing disease. This results in the need to increase the opioid dose in order to maintain the initial analgesic effect.

OIH refers to the development of hypersensitivity to painful stimuli observed upon chronic opioid administration, which leads to the paradox where the treatment prescribed to relieve pain will produce the opposite effect and cause a heightened pain sensation.

It can be difficult in the clinical setting to distinguish tolerance from OIH, particularly in the context of pain due to advanced cancer. This is because any dose increases could be caused by a reduction in the potency of the opioid (as seen with tolerance) or by lowering of the pain threshold (as in OIH). The clinical effect is the same since the development of either of these adverse effects will lead to increased pain, with the usual consequence of escalating doses.

Refer to ➔ Chapter 1, *Opioid pharmacology*, p. 12 for an overview of opioid receptors.

Tolerance

The effect of a drug may gradually diminish when it is given continuously or repeatedly, and it can develop within several weeks. Considerable

research *ex vivo* and *in vivo* (animals) illustrates the complexity and multitude of processes that underlie tolerance to opioids. Unfortunately, no single mechanism has been identified that can account for the degree of opioid tolerance typically observed. Tolerance is believed to occur due to adaptive changes that result in the need for dose escalation to maintain the same level of response. Numerous cellular and molecular mechanisms, including receptor desensitization, G-protein decoupling, β-arrestin recruitment, alterations in the expression of peripheral μ-opioid receptors (MORs), activation of N-methyl-D-aspartate (NMDA) receptors, and gut microbiota, have been postulated to contribute to the development of opioid analgesic tolerance. Genetics may also play a part, in terms of MOR structure. The extent to which some of these mechanisms influence opioid tolerance (and therefore clinical response) appears to depend on the cell type involved.

Tolerance to different pharmacological actions of opioids does not develop at the same rate or degree. This is termed *differential tolerance*. For example, tolerance to sedation and nausea often develops faster than tolerance to analgesia, whereas little tolerance, if any, develops to constipation (see ➔ *Opioid-induced bowel dysfunction* below). Persistence of opioid-induced constipation (OIC) can be explained by an altered cellular response in the colon involving β-arrestin, such that receptor activation continues. Tolerance to respiratory depression is believed to occur more slowly than tolerance to analgesia. In the management of cancer pain, provided the dose of opioid analgesic is titrated to the level of pain, mantra would suggest that significant respiratory depression is not expected to occur (since pain influences the respiratory drive). Addition of certain adjuvant analgesics, however, may attenuate the degree of opioid tolerance, with consequential development of opioid adverse effects such as sedation and respiratory effects (see ➔ Chapter 3, *Gabapentin*, p. 309).

Despite a wealth of animal studies, there is a paucity of information that unequivocally demonstrates tolerance to opioid-derived analgesia in cancer patients. A contributing factor to the complexity of *in vivo* administration of opioid drugs and the determination of analgesic tolerance is the number of clinically important differences among opioids. For example, given the array of sites that can mediate opioid analgesia, it is expected that differences in physicochemical and pharmacokinetic properties will influence pharmacodynamic responses. MOR agonists of low intrinsic efficacy (e.g. morphine) will occupy and engage a larger fraction of the available receptors to produce their effects than agonists with high intrinsic efficacy (e.g. fentanyl). It is believed that fentanyl produces less analgesic tolerance than morphine. The situation with buprenorphine is complex; it has low intrinsic activity, which is believed to minimize β-arrestin recruitment, resulting in reduced analgesic tolerance (and respiratory depression). In addition, buprenorphine is an opioid-like receptor-1 (ORL-1) agonist, a δ-opioid receptor (DOR) antagonist, and a κ-opioid receptor (KOR) inverse agonist. These properties are also believed to attenuate the development of tolerance (and OIH).

The development of analgesic tolerance can limit the clinical utility of opioid analgesics. Indeed, the progressive increase of opioid doses

driven by tolerance can induce or exacerbate undiagnosed OIH, which, in turn, may be misdiagnosed as progression of underlying disease. Given the complexity at the cellular level of opioid action and tolerance development, it is thought that a patient tolerant to one opioid could show only incomplete cross-tolerance to the new opioid. Incomplete cross-tolerance forms the basis for opioid switching (see *Equianalgesia and opioid switch*, p. 56).

Hyperalgesia

OIH can be broadly defined as a state of nociceptive sensitization caused by exposure to opioids. The risk of developing OIH depends not only on the dose of opioid taken, but also on factors such as gender, age, genotype, and cause of pain, i.e. each case will be unique. Clinically, hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality.

The exact mechanism of this paradoxical hypersensitivity to painful stimuli is still unclear. Narcotic bowel syndrome can be an alternative presentation of OIH. There is considerable overlap in the proposed mechanisms of tolerance and OIH, raising the possibility that they represent different facets of the same problem. It is believed a multitude of processes lead to an imbalance between pro- and anti-nociceptive activity. Pro-nociceptive pathways are believed to be activated after prolonged exposure to opioids. In effect, the pro-nociceptive activity can be considered to be the endogenous response to the exogenous effect (i.e. anti-nociceptive effect) of the opioid. Mechanisms include:

- increased expression of 6TM MOR (see Chapter 1, *Opioid pharmacology*, p. 12) and activation of NMDA receptors
- release of cholecystokinin (CCK) within the PAG–RVM pathways (reduces the activity of the descending anti-nociceptive pathway)
- activation of glial cells (opioids bind to Toll-like receptor 4 (TLR4) on glial cells, leading to the release of numerous inflammatory mediators)
- for morphine—accumulation of morphine-3-glucuronide.

Treatment options

Strategies, in no particular order and with very limited evidence of benefit for prevention or management of opioid tolerance and OIH, include (refer to the individual monographs in Chapter 3 for further information):

- adjuvant analgesia (e.g. NSAIDs, gabapentin, pregabalin)
- a combination of opioids (e.g. addition of low-dose methadone or tapentadol to current opioid)
- opioid switching (see *Equianalgesia and opioid switch*, p. 56)
- NMDA antagonists (e.g. ketamine).

Further reading

Martyn JAJ, Mao J, Bittner EA. Opioid tolerance in critical illness. *N Engl J Med*. 2019;**380**:365–78.

Mercadante S, Arcuri E, Santoni A. Opioid-induced tolerance and hyperalgesia. *CNS Drugs*. 2019;**33**:943–55.

Breakthrough cancer pain

Introduction

Pain is a common symptom of cancer, with a prevalence of up to 70% in patients with advanced disease. Background pain (also referred to as baseline or persistent pain) can, in most cases, be treated successfully with background analgesia, typically long-acting opioid formulations and adjuvant drugs such as gabapentin, pregabalin, or amitriptyline.

In addition, cancer patients can experience pain that is superimposed on background pain. This can occur as a result of:

- poorly controlled background pain (i.e. continued dose titration, or addition of an adjuvant is warranted)
- incident pain (precipitated by movement or activity), which can be:
  - *volitional* (i.e. predictable pain caused by voluntary event, e.g. walking, wound dressing)
  - *non-volitional* (i.e. unpredictable pain caused by involuntary actions, e.g. coughing, sneezing)
- spontaneous pain (unpredictable, with no identifiable precipitant; potentially neuropathic in origin)
- end-of-dose failure.

Except for end-of-dose failure, these exacerbations have collectively been described as *breakthrough pain*. End-of-dose failure that occurs regularly towards the end of the dosing interval for regularly administered opioids can be potentially managed by increasing the dose or the frequency of administration (e.g. fentanyl may occasionally be administered every 48 hours if end-of-dose failure is identified). There is no universally accepted definition of breakthrough pain and a lack of consensus unquestionably leads to inadequate assessment and subsequent suboptimal treatment, which impacts on the patient's quality of life. Traditionally, treatment of breakthrough pain has been guided by the WHO's analgesic ladder where fixed doses of oral standard-release opioids (usually one-sixth to one-tenth of the background analgesic dose) are administered to treat any exacerbation of pain, irrespective of the cause. Adjustments to the background dose are considered, dependent on the number of doses of standard-release opioid given in the preceding 24 hours, without any regard to the nature of the exacerbation. This approach could lead to rapid development of opioid toxicity. It is noteworthy that this recommendation for the management of breakthrough pain remains in the updated version of the WHO guidelines for management of cancer pain.

In an attempt to improve the approach to treatment of pain that 'breaks through' background analgesia in cancer patients, the term *breakthrough cancer pain* (*BTcP*) has been introduced. This essentially proposes that patients with poorly controlled background pain need different management to those with incident or spontaneous pain.

Definition

As mentioned earlier, there is no universally accepted definition of BTcP, although it is generally agreed that the patient must have stable and controlled background pain that is distinguishable from the painful episode. In addition, this painful episode should have a fast onset and a short duration.

The Association for Palliative Medicine of Great Britain and Ireland (APM) describes BTcP as a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, experienced by patients who have relatively stable and adequately controlled background pain.

Characteristics of breakthrough cancer pain

Clinical features of cancer pain, including BTcP, can vary among patients in that some patients may only experience one type of pain, whereas others may experience several distinct pains. Furthermore, the clinical features can vary within a patient during the course of the disease.

BTcP is usually of moderate to severe intensity and the pathophysiology is often, but not always, the same as background pain; it can be neuropathic or nociceptive, or a combination of both. The reported prevalence of BTcP varies widely (19–95%), mainly due to a lack of accepted definition and different study designs. Nonetheless, it has been suggested that BTcP:

- typically reaches a maximum intensity (median 5–10 minutes)
- has a reported short duration of 30–45 minutes, with a mean of three episodes per day.

Untreated BTcP could have a profound impact on quality of life and a number of consequences have been reported:

- impairment of daily activities, e.g. walking, working
- anxiety and depression
- interference with sleep
- reduced social interaction
- higher pain severity
- dissatisfaction with overall pain management
- greater healthcare costs.

Management

The patient must be assessed in order to differentiate between exacerbations of *poorly controlled background pain* and *incident/spontaneous pain* (i.e. BTcP) because subsequent treatment modalities are completely different. It is important that BTcP is considered separately from background pain and its treatment is individualized. Treatment of BTcP primarily involves pharmacotherapy, although consideration should be given to non-pharmacological interventions such as massage, application of heat or cold, and distraction or relaxation techniques. Successful management of BTcP includes the following:

- assessment of characteristics of both the pain (e.g. temporal profile, aetiology) and the patient (e.g. disease, preferences)
- treatment of the underlying cause (e.g. radiotherapy, chemotherapy, surgery)
- avoidance of precipitating factors
- adjustment of background analgesia (e.g. addition of adjuvant analgesics)
- use of rescue medication
- reassessment.

Use of opioids for rescue medication is considered the treatment of choice for BTcP. Note that opioids are unlikely to control all types of BTcP and alternative strategies may need to be adopted. There is no correlation

between the background analgesic dose and the rescue dose of opioid needed to successfully control BTcP. This must be determined by individual titration.

The choice of opioid and formulation for this condition continues to be a controversial issue, which is undoubtedly a consequence of the lack of a clear definition, coupled with the relatively high acquisition costs of the relatively newer, fentanyl-based products. Once BTcP has been diagnosed, pharmacological treatment should focus on the temporal characteristics of the pain episode. Oral standard-release opioid formulations are unlikely to be the ideal option for most episodes of BTcP that resolve after 30–45 minutes. The pharmacokinetic profiles of oral opioids (onset of action 20–30 minutes, peak analgesia 60–90 minutes) do not complement the temporal characteristics of these brief episodes of BTcP. There is also the prolonged duration of action to consider (e.g. up to 4 hours with morphine), which can potentially manifest as adverse effects such as drowsiness. Nonetheless, such an approach would be suitable for BTcP of duration of more than an hour or in situations where anticipatory treatment of an identifiable cause is both possible and acceptable; for example, BTcP precipitated after a period of walking may be successfully managed with oral standard-release opioid formulations. In such cases, a rescue dose (of standard-release formulation) based on 5 to 20% of the background opioid dose may suffice.

For many brief episodes of BTcP (i.e. lasting <1 hour), the use of a short-acting opioid with quick onset of action may be the most appropriate treatment. There are several products licensed specifically for the treatment of BTcP (refer to ➔ Chapter 3, *Fentanyl (transmucosal)*, p. 280). In addition, there is an unlicensed alfentanil product available for intranasal use (see ➔ Chapter 3, *Alfentanil*, p. 101).

Non-opioid analgesics (e.g. paracetamol, NSAIDs, ketamine) and non-pharmacological techniques (e.g. massage, heat/cold, relaxation) have been used to treat BTcP, although there is presently a dearth of evidence to support their use. A variety of interventional techniques can be considered for the treatment of BTcP (e.g. neural blockade, neuroablation).

Further reading

Davies A, Buchanan A, Zeppetella G, *et al.* Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manage*. 2013;**46**:619–28.

Davies AN, Dickman A, Reid C, Stephens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain*. 2009;**13**:331–8.

Mercadante S, Portenoy RK. Understanding the chameleonic breakthrough cancer pain. *Drugs*. 2021;**81**:411–18.

Equianalgesia and opioid switch

Opioids remain the most effective analgesics known for many types of pain and are arguably the mainstay of pain management in patients with cancer. Morphine is generally considered to be the opioid of first choice in palliative care for several reasons such as familiarity, low cost, available formulations, and proven effectiveness.

Opioid responsiveness has been defined as the degree of analgesia achieved as the dose is titrated to an endpoint, defined either by intolerable adverse effects or the occurrence of acceptable analgesia. It can be influenced

(but not wholly defined) by the drug's potency (see ➔ Chapter 1, *Pharmacodynamics*, p. 10). Potency is determined by pharmacokinetic (the ability of the drug to reach the receptor), pharmacodynamic (e.g. affinity, intrinsic efficacy), and pharmacogenetic factors. Drug interactions and comorbidity can also impact on a drug's potency, as can regular use through the development of tolerance (see ➔ *Opioid-induced hyperalgesia and tolerance*, p. 51). *Relative potency* is defined as the ratio of drug doses necessary to obtain roughly equivalent effects; this can apply to two different drugs or to two different routes of administration for the same drug. Using this definition, relative analgesic potency can be used to determine an *equianalgesic ratio* between drugs or between routes of administration. The equianalgesic ratio determines equipotency, or the dose at which two opioids (or two routes of administration of the same opioid) provide approximately the same pain relief.

Table 2.4 illustrates commonly used equianalgesic values, along with manufacturers' recommendations where applicable. Equianalgesic tables serve as an approximate guide only because there are inherent limitations since equianalgesic doses are difficult to ascertain due to wide interpatient variations (e.g. comorbidity, drug interactions, genetics) and non-interchangeability of products. There is a clear disparity in the literature, with many equianalgesic values being derived largely from expert opinion, studies in non-cancer patients, single-dose studies, or studies that included populations with little prior opioid exposure. Such approaches have failed to consider patient-specific variables (i.e. comorbidity, drug interactions, and genetics) or assess the effects of tolerance. Given the complexity at the cellular level of opioid action and tolerance development, it is thought that a patient tolerant to one opioid will show only incomplete cross-tolerance to the new opioid. Incomplete cross-tolerance forms the basis for opioid switching. This does, however, have implications when calculating the dose of the new opioid. A further complication is the possibility that equianalgesia values are not bidirectional. While it is assumed the equianalgesic ratio applies in both directions, clinical studies suggest this may not always be the case (see morphine to hydromorphone in Table 2.4).

Opioid switch (also known as opioid substitution, or rotation) is the changing from one opioid to another or changing an opioid's route of administration. It may become necessary to change opioid, or to another route of administration, for several reasons, including:

- deterioration in condition
- drug interactions
- dysphagia
- intolerable adverse effects (e.g. nausea, constipation, hallucinations, myoclonus)
- malabsorption
- patient request (e.g. reduction of tablet load)
- poor analgesic response despite dose titration (e.g. neuropathic pain, cancer-related bone pain)
- renal impairment
- tolerance or OIH.

Before undertaking opioid switch, consider simple measures such as:
- adjuvant medications to improve undesirable effects, e.g. peripherally acting MOR antagonist (PAMORA) for OIC
- check for drug interactions (e.g. clarithromycin and fentanyl)
- dose reduction
- rehydration.

The prescriber should use clinical judgement when deciding on the dose of the new opioid. There are several steps that must be considered before deciding on an appropriate dose:
- Patient factors:
  - co-morbidity (e.g. hepatic or renal impairment)
  - current pain status.
- Current treatment:
  - dose of opioid to be changed (including rescue doses taken for pain flares)
  - drug interactions (e.g. converting from morphine to an equianalgesic dose of fentanyl in a patient taking carbamazepine may result in worsening pain).
- Equianalgesic table:
  - determine the dose of the new treatment regimen as per the equianalgesic ratio
  - note that methadone is excluded from the table due to its complex pharmacokinetics (see ➔ Chapter 3, *Methadone*, p. 431).
- Dose adjustment:
  - A degree of tolerance to the effects of opioids is expected to occur with chronic use. One of the underlying principles of opioid switch is that tolerance to the effects of the new opioid will not be as pronounced. As such, if the dose calculated using the equianalgesic ratio is not reduced, the patient may be at risk of adverse effects from the new opioid. Clearly, this does not apply when solely switching routes of administration. Nonetheless, a dose reduction may still be warranted due to interpatient variation reported in the bioavailability of the various opioids (e.g. oral bioavailability of morphine ranges from 15% to 69%; mean 40%).
  - Consider reducing the equianalgesic dose derived from the table by 25 to 50% when switching opioids; it is preferable to under-dose the patient and use rescue medication for any shortfalls. When only changing the route of administration of the opioid, a lesser reduction may be considered (e.g. 20%).
  - The suggested equianalgesic dose becomes gradually less precise as the dose increases, even more so if there has been recent rapid dose escalation; a larger dose reduction may be preferable in this situation.
  - Ensure appropriate rescue medication is prescribed to ensure titration of background analgesia.
- Review:
  - Regular reassessment of the pain during the hours following the opioid switch is vital to ensure safe and effective pain management.

Table 2.4 Equianalgesic table

Opioid	Suggested conversion ratio to ORAL morphine	Notes
Alfentanil (SUBCUT)	1:30	
Buprenorphine (TD)	1:100	Manufacturer recommends 1:75 to 1:115 after multiple doses in chronic pain
Codeine (PO)	10:1	
Diamorphine (SUBCUT)	1:3	
Dihydrocodeine (PO)	10:1	
Fentanyl (TD)	1:100	Manufacturer recommends 1:150
Hydromorphone (PO)	1:5	Manufacturer recommends 1:7.5
Hydromorphone (SUBCUT)	SUBCUT *morphine* to SUBCUT *hydromorphone*, use 5:1 SUBCUT *hydromorphone* to SUBCUT *morphine*, use 1:4	
Methadone (PO)	Refer to monograph in ➔ Chapter 3.	
Morphine (SUBCUT)	1:2	Studies suggest a 1:3 ratio is also effective
Oxycodone (PO)	1:1.5	Manufacturer recommends 1:2
Oxycodone (SUBCUT)	1:2	PO oxycodone:SUBCUT oxycodone is 1.5:1. The SmPC states 2:1
Tapentadol (PO)	3.3:1	Indirect derivation, based on 5:1 PO tapentadol:PO oxycodone. NB—a higher ratio may be expected in management of acute pain
Tramadol	Refer to monograph in ➔ Chapter 3.	

Examples:

Morphine PO 60mg BD = alfentanil 4mg via CSCI over 24 hours.

Morphine PO 60mg BD = oxycodone PO 40mg BD.

Morphine PO 30mg BD = fentanyl TD 600 micrograms in 24 hours = 25 micrograms/hour patch.

Morphine PO 30mg BD = buprenorphine TD 840 micrograms in 24 hours = 35 micrograms/hour patch (*based on 75:1 ratio*).

SUBCUT, subcutaneous; TD, transdermal; PO, oral.

Further reading

Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. *J Pain Symptom Manage*. 2009;**38**:426–39.

McPherson ML. Why equianalgesic tables are only part of the answer to equianalgesia. *Ann Palliat Med*. 2020;**9**:537–41.

Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: a systematic review. *Palliat Med*. 2011;**25**:504–15.

Neuropathic pain

Neuropathic pain is caused by a lesion or disease affecting the somatosensory system. It is common in cancer, reportedly affecting up to 40% of patients. It results from direct damage to the nervous system from a primary tumour or metastases (e.g. thoracic tumour affecting the brachial plexus or bone metastasis causing vertebral collapse), or from cancer treatment such as CIPN, radiotherapy, or surgery (e.g. thoracotomy). Symptoms of neuropathic pain can be described as positive (spontaneous or evoked pain) and negative (loss of sensation). Evoked pain can result from allodynia or hyperalgesia. Patients may describe neuropathic pain as shooting, sharp, pins and needles, electric shocks, stabbing, or itching.

Evidence-based treatment of cancer-related neuropathic pain is limited. Non-pharmacological interventions (e.g. transcutaneous electrical nerve stimulation (TENS), acupuncture, psychological) should be considered alongside pharmacological treatment. While international guidelines are available, there is no consensus about which treatment represents the first-line approach. A systematic review examined the role of adjuvant analgesics (drugs with a primary indication other than pain, but with analgesic properties under certain circumstances) in the pharmacological management of cancer pain, both mixed and purely neuropathic. The authors concluded that there was low-quality evidence that gabapentin, pregabalin, amitriptyline, and venlafaxine were effective in reducing pain intensity in patients with cancer pain. Pharmacological treatment invariably comprises an opioid and an adjuvant analgesic (or co-analgesic). Contrary to the common belief of poor efficacy in neuropathic pain, opioids have been found useful in several neuropathic conditions.

Pharmacological management

The principles relating to opioid prescribing described in the latest WHO recommendations for cancer pain relief should be followed. Note that the WHO makes no recommendation for the use of adjuvant analgesics. Strong opioids should be titrated against response. If the patient experiences intolerable undesirable effects or poor efficacy during titration with an opioid:

- consider opioid switch
- add one of the following to the regimen: gabapentin, pregabalin, amitriptyline, duloxetine, or venlafaxine
  - nortriptyline may be preferred over amitriptyline in the elderly.
- if ineffective, consider adding, or swapping to, an adjuvant from a different therapeutic class
- if nerve compression is suspected, a trial of a short course of corticosteroids could be considered (e.g. dexamethasone 8mg once daily (OD) for 5 days)
- consider referral to anaesthetic pain specialists if the patient is not responding to pharmacological management.

Other options, in no particular order and with very limited evidence of benefit for treatment of cancer-related neuropathic pain, include (refer to the individual monographs in ➲ Chapter 3 for further information):

- clonazepam
- ketamine (specialist use only)

- lidocaine (parenteral—specialist use only)
- lidocaine (topical—note that any benefit may be explained as a placebo effect)
- methadone (as the main opioid, or in low doses in combination with another opioid)
- tapentadol (alone, or in combination with another opioid).

Further reading

Fallon M, Giusti R, Aielli F, *et al.*; ESMO Guidelines Committee. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;**29**(Suppl 4):iv166–91.

van den Beuken-van Everdingen MH, de Graeff A, Jongen JL, Dijkstra D, Mostovaya I, Vissers KC; national guideline working group 'Diagnosis treatment of cancer pain'. Pharmacological treatment of pain in cancer patients: the role of adjuvant analgesics, a systematic review. *Pain Pract*. 2017;**17**(3):409–19.

Managing nausea and vomiting

Many patients with advanced cancer (up to 70% in the last week of life) can experience nausea and vomiting. There are many causes, some of which are reversible (see Box 2.3). Antiemetic guidelines are based on largely on expert opinion or on moderate to weak evidence at best. Ideally, the choice of an antiemetic will depend on the cause(s) of nausea and vomiting. It is unlikely that one antiemetic will treat all cases, especially as most patients have multiple, and often irreversible, causes.

Box 2.3 Common causes of nausea and vomiting in advanced cancer

Anxiety	Gastritis
Autonomic neuropathy	Gastroparesis
Biochemical (e.g. ↑ Ca^{2+}, ↓ Na^{+})	Infection
Bowel obstruction	Pain
Constipation	Raised intracranial pressure
Cough	Renal failure
Drugs	Vestibular disturbance

A variety of neurotransmitters are involved in the vomiting pathway and currently no available drug will antagonize all receptor sites, nor is there a universal agent that will block the final common pathway, the output from the vomiting centre. In addition, many patients may have multiple, irreversible causes. A mechanistic approach, based on the neuropharmacology of emesis, is often suggested, although there is no evidence to support or refute this. Initial treatment should involve the *regular* prescription of *one* antiemetic (as opposed to as-necessary (PRN) use), titrated to its maximum dose. A systematic review focusing on antiemetics in advanced cancer recommended the use of **either** metoclopramide **or** haloperidol as first-line choices, with levomepromazine **or** olanzapine as second-line options. Nonetheless, a combination of agents may have a greater antiemetic action than a single drug. In such cases, the drugs chosen should have synergistic, rather than additive or opposing, pharmacological actions. Suggested treatment approaches are shown in Table 2.5.

Further reading

Davis M, Hui D, Davies A, *et al*. MASCC antiemetics in advanced cancer updated guideline. *Support Care Cancer*. 2021; **29**(12):8097–107.

Davis M, Hui D, Davies A, *et al*. Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. *Support Care Cancer*. 2021; **29**(12):8089–96.

Madariaga A, Lau J, Ghoshal A, *et al*. MASCC multidisciplinary evidence-based recommendations for the management of malignant bowel obstruction in advanced cancer. *Support Care Cancer*. 2022; **30**(6):4711–28.

Table 2.5 Suggested drug choices for nausea and vomiting

Cause	First-line drug	Second-line drug*	Notes
Chemoreceptor trigger zone (e.g. drugs, hypercalcaemia)	Haloperidol or Metoclopramide	Levomepromazine	–
Gastric stasis	Metoclopramide	–	Antimuscarinic drugs and 5-HT_3 antagonists may reduce the prokinetic effect
Gastric irritation (e.g. drugs, tumour infiltration)	Metoclopramide	Levomepromazine or Ondansetron	Consider PPI if NSAID-induced
Total bowel obstruction	Octreotide	Add anticholinergic (e.g. hyoscine butylbromide or glycopyrronium)	Consider adding levomepromazine, haloperidol, or ondansetron in difficult cases. Dexamethasone may offer some benefit. Consider a nasogastric tube or venting gastrostomy
Partial bowel obstruction (without colic)	Metoclopramide	Olanzapine	Dexamethasone may offer some benefit. Consider faecal softener (e.g. sodium docusate)
Raised intracranial pressure	Cyclizine and dexamethasone	Levomepromazine and Dexamethasone	Do not administer dexamethasone and levomepromazine together via the same CSCI
Unknown	Cyclizine ± haloperidol or Levomepromazine	Olanzapine	–

* Substitute the first-line drug with the second-line agent unless the table states otherwise.

PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; CSCI, continuous subcutaneous infusion.

Management of constipation in advanced cancer

Constipation is a common problem in patients with advanced cancer. Since constipation is a subjective experience, it should be defined by the patient, not the practitioner. Patients with an European Cooperative Oncology Group (ECOG) performance status of 3 or 4 are at high risk of developing constipation (i.e. patients confined to bed or chair for >50% of waking hours or totally confined to bed or chair). The reported prevalence of constipation in advanced cancer patients ranges between 32% and 87%.

Causes of constipation can be primary (i.e. functional dysfunction) or secondary (i.e. disease- or medication-related). Common causes of constipation are shown in Box 2.4. Symptoms range from those caused as a direct result of constipation (e.g. bloating, abdominal discomfort) to local (e.g. overflow diarrhoea, faecal impaction, GI obstruction) and systemic (e.g. confusion, headache, dyspepsia).

Box 2.4 Common causes of constipation in advanced cancer

- Anal fissure
- Bowel obstruction
- Brain tumour
- Confusion
- Dehydration
- Dementia
- Depression
- Drugs (e.g. anticholinergics, opioids, 5-HT_3 antagonists)
- Environmental (e.g. lack of privacy)
- Haemorrhoids
- Hypercalcaemia
- Hypothyroidism
- Reduced physical activity
- Low dietary fibre
- Spinal cord compression
- Weakness

Opioid-induced bowel dysfunction

Opioid-induced bowel dysfunction (OIBD) represents a symptom complex that develops as a consequence of chronic opioid use and reflects the impact of opioids on the GI tract. The effects of opioids in the GI tract are largely mediated by the MOR, but there are regional differences in the action of opioids in the small and large intestines. Specifically, while tolerance can develop to the effects on motility in the upper GI tract, this is not the case in the colon; the net result is persistent constipation with prolonged opioid use. This apparent anomaly can be explained by differences in activity of β-arrestin between the colon and small intestine (see Chapter 1, *Opioid pharmacology*, p. 12 and *Opioid-induced hyperalgesia and tolerance*, p. 51).

OIC is the most common OIBD. The risk of OIC may vary between opioids (e.g. reportedly lower with buprenorphine and tapentadol than with morphine) but is independent of the dose. Other symptoms of

OIBD include abdominal distension, dysphagia, dyspepsia/reflux, nausea/vomiting, incomplete evacuation, and abdominal pain.

Opioids interfere with normal GI function and cause constipation by:

- decreasing small bowel motility
- decreasing electrolyte and water secretion from epithelial cells
- increasing electrolyte and water absorption
- increasing anal sphincter tone.

For these reasons, the management of OIC is different to that of other causes of constipation. OIC has been defined in the Rome IV diagnostic criteria as new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy that must include two or more of the following:

- straining during more than one-quarter (25%) of defecations
- lumpy or hard stools (Bristol Stool Form Scale (BSFS) 1–2) in more than one-quarter (25%) of defecations
- sensation of incomplete evacuation in more than one-quarter (25%) of defecations
- sensation of anorectal obstruction/blockage in more than one-quarter (25%) of defecations
- manual manoeuvres to facilitate more than one-quarter (25%) of defecations (e.g. digital evacuation, support of the pelvic floor)
- fewer than three spontaneous bowel movements per week.

Treatment recommendations for constipation

- Treat reversible causes of constipation and minimize any potential aggravating factors. For example, it may be possible to withdraw medication that has caused secondary constipation. Non-drug measures, such as ensuring adequate privacy or correct toileting position (may be aided by the use of a footstool), may facilitate defecation.
- There is no evidence to suggest that lifestyle changes (such as increased dietary fibre or increased exercise) improve constipation in patients with advanced cancer.
- Conventional laxatives should be considered as first-line treatment in patients with constipation (primary and secondary, including OIC). There is no evidence to support the choice of laxative in palliative care patients, particularly the traditional approach of stimulant plus softener.
- If an adequate response to optimal dosing of first-line treatment is not achieved, combination with, or switch to, a different class of laxative is suggested (see Table 2.6).
- PAMORAs should always be considered in patients with OIC who have failed to respond to traditional laxatives. Opioid switch as a treatment option to reduce the incidence of OIC may help, but the evidence is limited.
- There are currently two oral PAMORAs licensed in the UK: naldemedine and naloxegol. Methylnaltrexone is only available in parenteral form. The National Institute for Health and Care Excellence (NICE) has reviewed both oral PAMORAs and issued favourable technology appraisals. See the individual monographs for more details.

- The exact time when a PAMORA can be initiated may also differ, depending on the interpretation of recommendations.
  - For *naloxegol*, the SmPC and NICE both suggest that it can be introduced as an option for patients whose OIC has not adequately responded to laxatives. Inadequate response is defined as OIC symptoms of at least moderate severity in at least one of the four stool symptom domains (i.e. incomplete bowel movement, hard stools, straining, or false alarms) while taking at least one laxative class for at least 4 days during the previous 2 weeks.
  - For *naldemedine*, there is no mention of how long a patient must have been taking a laxative before starting. In these circumstances, reference to the Rome IV criteria (see ➲ *Opioid-induced bowel dysfunction*, p. 64) is suggested.
- Constipation in patients with advanced cancer is likely to be multifactorial in aetiology. It is probable that patients may need laxatives and a PAMORA.
- Rectal interventions (i.e. enemas and suppositories) are generally reserved for patients who have failed to respond to the above measures. The evidence for such interventions is weak. Enemas can be helpful if there is stool in the descending colon, whereas suppositories may be selected if there is stool in the rectum. Certain international guidelines (e.g. Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO)) state that enemas and suppositories are contraindicated for use in patients with neutropenia or thrombocytopenia, although the SmPCs of such products do not state this.
- All patients should be regularly reassessed.

Table 2.6 Classification of laxatives

Bulk-forming agent	Increases faecal mass, leading to intestinal distension and subsequent stimulation of peristalsis. Not recommended for opioid-induced constipation due to risk of colic and rarely obstruction Example: ispaghula husk
Stool softener	Allows penetration of water into the stool Example: docusate, arachis oil
Osmotic laxative	Draws water into the gut lumen, preventing stool from becoming hard Example: lactulose, macrogol 3350, magnesium hydroxide
Stimulant laxative	Directly promotes peristalsis and reduces colonic water absorption Example: senna, bisacodyl, co-danthramer

Further reading

Davies A, Leach C, Caponero R, *et al.* (2020) MASCC recommendations on the management of constipation in patients with advanced cancer. *Support Care Cancer*. 2020;**28**(1):23–33.

Larkin PJ, Cherny NI, La Carpia D, *et al.*; ESMO Guidelines Committee. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018;**29**(Suppl 4):iv111–25.

QT interval

The QT interval is primarily a measure of ventricular repolarization and is described as the time taken from the start of the Q wave to the end of the T wave on a standard 12-lead electrocardiogram (ECG) (see Fig. 2.1). As the time for ventricular repolarization (and therefore QT interval) is dependent on the heart rate, it is shorter at high heart rates and longer at slower heart rates. To account for this, the QT corrected for heart rate, or QTc, is often used:

$$QTc = \frac{QT}{\sqrt{RR\ \text{interval}}}$$

There is no consensus currently regarding what is considered a 'normal' range for QTc, though, in general, most studies have adopted the upper limit of normal as being 450ms. Some studies have differentiated by gender and suggested that the QTc is 10–20ms longer in women. It is generally accepted that a normal value for QTc is ≤440ms in men and ≤460ms in women. A prolonged QTc is widely associated with a specific form of polymorphic ventricular failure (i.e. torsades de pointes) and possible sudden cardiac death. Women are more susceptible than men to drug-induced QTc prolongation. Renal, cardiac, and hepatic failure are also risk factors. QTc prolongation can be either due to a congenital cardiac syndrome or acquired due to one or more of the following causes:

- drugs
- cardiac pathology (heart failure, ischaemia, myocarditis)
- electrolyte abnormality (hypokalaemia, hypomagnesaemia)
- cerebrovascular disease (subarachnoid haemorrhage, ischaemic stroke)
- severe bradycardia (especially complete heart block)
- hyperthyroidism/hypothyroidism.

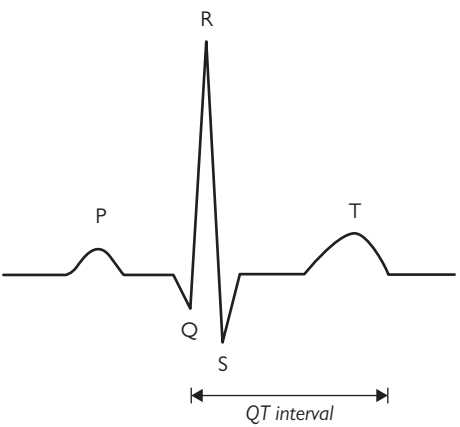


Fig. 2.1 ECG with QT interval marked.

Relevance to palliative care

A large number of drugs used for symptom control in palliative care have been associated with causing QT interval prolongation. It is therefore imperative that a common-sense approach to medication review and selection is adopted when assessing a patient and making prescribing decisions. For example, if a patient is thought to be in the last days of life, performing a 12-lead ECG prior to starting medication known to prolong the QT interval is likely irrelevant. If, however, the same medication was to be initiated in a patient much earlier in the disease trajectory, such an investigation would be prudent.

Drug-related QT interval prolongation

The mechanism by which drugs cause QT interval prolongation is thought to be due to the blockade of cardiac potassium channels. This effect is usually observed within several days of starting the medication. Additionally, there is the potential for drug interactions to increase the risk of QT prolongation. There are three main mechanisms by which this can occur:

- pharmacodynamic drug interaction (co-prescription of two or more drugs known to increase the QT interval, leading to an additive effect)
- pharmacokinetic drug interaction (where a drug that does not prolong the QT interval itself reduces clearance and therefore increases the concentration of a QT-prolonging drug)
- drug-induced electrolyte imbalances (i.e. hypokalaemia or hypomagnesaemia) which can increase the risk of QT prolongation

To minimize the risk of long QT syndrome when initiating a new medication, prescribers may elect to correct modifiable risk factors (i.e. rectification of hypokalaemia/hypomagnesaemia) prior to initiation. The patient's current medication list should also be reviewed to ascertain if there are any other medications known to cause long QT syndrome currently prescribed. If there are, these should be reviewed and stopped, or changed if clinically acceptable. If the drug to be initiated is known to cause QT interval prolongation, a baseline ECG should be performed prior to the first dose, and repeated once the new drug has reached steady state (generally after 4–5 half-lives). If significant QT prolongation is observed (i.e. an increase of >50ms or an absolute value of >500ms), any electrolyte imbalances should be checked and corrected, and a repeat ECG performed. If QT prolongation is not resolved, dose reduction or treatment cessation should be considered.

CredibleMeds® (https://www.crediblemeds.org/) is a useful free resource that maintains a list of drugs suspected or known to prolong the QT interval. This resource categorizes medications into one of four categories, highlighting their risk of causing QTc prolongation (see Table 2.7). These categorizations have been incorporated into the drug monographs found in Chapter 3 of this book. The list produced by *CredibleMeds*® is periodically updated; when there is new evidence available, a drug's risk category may change.

Table 2.7 *CredibleMeds*® risk categories for drugs that prolong QT interval and induce torsades de pointes

Categorization		Definition
Known risk of TdP		Drugs that prolong QT interval AND are associated with a known risk of TdP when taken as directed
Possible risk of TdP		Drugs that prolong QT interval BUT currently lack evidence for a risk of TdP when taken as directed
Conditional risk of TdP	Risk under certain conditions	Drugs associated with TdP, BUT only under certain conditions of use (e.g. excessive dose, hypokalaemia, hypomagnesaemia, bradycardia, or when taken with other QT-prolonging drugs)
	Drug creating conditions for risk	Drugs associated with TdP because they create conditions that facilitate or induce TdP (e.g. loop diuretics, proton pump inhibitors, drugs that block metabolism of QT-prolonging drugs or cause bradycardia)
Special risk*		Drugs that do not prolong QT interval per se but which have adrenergic actions that create a risk of TdP for patients with congenital long QT syndrome

* Special risk category is not referred to in this book.

TdP, torsades de pointes.

Reproduced from Woosley RL, Heise CW, Gallo T, *et al*., CredibleMeds, QTdrugs List, Copyright (2022), with permission from CredibleMeds®. Available from https://crediblemeds.org/blog/clarification-crediblemedsr-tdp-risk-categories [Accessed 21 February 2022].

Further reading

Hardy JR, Bundock D, Cross J, *et al*. Prevalence of QTc prolongation in patients with advanced cancer receiving palliative care—a cause for concern? *J Pain Symptom Manage*. 2020;**59**(4):856–63.

Khatib R, Sabir FRN, Omari C, Pepper C, Tayebjee MH. Managing drug-induced QT prolongation in clinical practice. *Postgrad Med J*. 2021;**97**(1149):452–8.

Nachimuthu S, Assar MD, Schussler JM. Drug-induced QT interval prolongation: mechanisms and clinical management. *Ther Adv Drug Saf*. 2012;**3**(5):241–53.

Woosley RL, Heise CW, Gallo T, Tate J, Woosley D, Romero KA. QTdrugs list. 2022. Available from: https://www.crediblemeds.org. Accessed 21 February 2022.

Polypharmacy and deprescribing

Introduction

Advanced illness is often accompanied by acute symptoms (e.g. pain, dyspnoea, fatigue) and patients may be prescribed medications to provide symptomatic relief. Additionally, such patients often have multiple comorbidities requiring treatment with long-term medication. These factors mean that patients with advanced illness are commonly subjected to polypharmacy.

The increased burden of pharmacotherapy placed upon patients with advanced illness can result in non-adherence to prescribed treatment and increase the risk of drug-associated adverse events due to drug–drug interactions or drug–patient interactions (e.g. declining renal or hepatic function).

To limit the likelihood of polypharmacy-induced adverse events, it is recommended that patients with advanced illness regularly receive medication reviews to identify and stop or reduce the dose of potentially inappropriate or unnecessary medications. This is termed deprescribing.

The deprescribing process

To maximize the success of deprescribing, communication of actions and follow-up with patients, their carers, and other healthcare professionals is essential. To aid the deprescribing process, the 5-step protocol designed by Scott *et al*.[1] (see Table 2.9) may be useful.

Available deprescribing frameworks

Upon identifying patients who are struggling to cope with their medication burden, and who agree upon a need for deprescribing, dose reduction or withdrawal of medications should be performed in an evidence-based manner, with use of validated clinical algorithms where available. Table 2.8 lists some widely used algorithms to assist in deprescribing.

Table 2.8 Algorithms to assist deprescribing

Algorithm	Description
Beers criteria[2]	A list of medications thought to be less appropriate for use in the elderly
STOPP/START[3]	A list of prescribing scenarios that are less appropriate in the elderly
PolyPharmacy guidance[4]	A Scottish online tool which provides deprescribing evidence summaries for specific groups of medicines
OncPal deprescribing guideline[5]	A palliative care-specific deprescribing guideline which highlights medications that are potential targets for discontinuation

Table 2.9 The 5-step deprescribing protocol

Step	Process
1	Review all medications (both prescribed and over-the-counter) and identify rationale for each one
2	Appraise the overall risk of medication-induced harm and evaluate how intensive a deprescribing intervention is required
3	Assess each medication for its deprescribing potential: • Is the indication for prescribing relevant? • Is the medication being used to ameliorate side effects of another medication? • Does the actual or potential harm of the medication outweigh the intended benefit? • Is the medication inadequately controlling the intended disease/symptom? • Has the intended disease/symptom completely resolved, rendering the medication obsolete? • Is the medication prescribed to prevent a disease/event that is unlikely to occur or confer any benefit over the patient's remaining expected lifespan? • Is the patient currently finding their usual medication regime burdensome?
4	Prioritize medicines suitable for deprescribing
5	Agree, implement, then monitor the deprescribing regimen

Source: data from *JAMA Intern Med.*, **175**(5), Scott IA, Hilmer SN, Reeve E, *et al.*, Reducing inappropriate polypharmacy: the process of deprescribing, pp. 827–834, Copyright (2015), American Medical Association.

Potential barriers and enablers of deprescribing

A recent systematic review by Paque *et al.*[2] identified that there are three different types of barriers and enablers to deprescribing of medication in patients with advanced illness. The most common factors were organizational support, multidisciplinary communication and collaboration, and communication with patients and their families. Table 2.10 summarizes the barriers and enablers identified in this systematic review.

Table 2.10 Barriers and enablers to deprescribing of medication in patients with advanced illness

Type of barrier or enabler	Examples of barriers	Examples of enablers
Organizational	• Shortage of staff in a care environment • Inadequate training of staff • National healthcare system	• Drugs and therapeutics committee meetings • Pharmacist-led medication reviews • Patient resistance to taking medication
Professional	• Perceived difficulty or resistance to engaging by patient or patient's family • Perceived benefits of medications and negative effects of deprescribing • Negative reactions of other healthcare professionals towards the prescriber • Interdisciplinary communication	• Communication of risk/benefits of medication with patient or patient's family • Acknowledgement that medications are burdensome • Interventions • Interdisciplinary communication
Patient-/family-related	• Patient's perception of potential risks and concerns • Mismatch of expectations between healthcare professional and patient and carer regarding treatment	• Patient's perception of potential benefits • Volume of medications • Swallowing difficulties • Shared decision-making

Adapted from *Palliat Med*, **33**(1), Paque K, Stichele RV, Elseviers M, *et al*., Barriers and enablers to deprescribing in people with a life-limiting disease: A systematic review, pp. 37–48, Copyright (2019), with permission from SAGE Publications.

References and further reading

1. Scott IA, Hilmer SN, Reeve E, *et al*. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015;**175**(5):827–34.
2. Paque K, Vander Stichele R, Elseviers M, *et al*. Barriers and enablers to deprescribing in people with a life-limiting disease: a systematic review. *Palliat Med*. 2019;**33**(1):37–48.

Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. *Age Ageing*. 2021;**50**(2):465–71.

Lindsay J, Dooley M, Martin J, *et al*. The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. *Support Care Cancer*. 2015;**23**(1):71–8.

NHS Scotland. Polypharmacy guidance—medicines review 2019. Available from: http://www.polypharmacy.scot.nhs.uk/polypharmacy-guidance-medicines-review/. Accessed 2 June 2021.

The 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;**67**(4):674–94.

Discontinuing and/or switching antidepressants

Discontinuation

If a patient has been taking antidepressants for 8 weeks or more, the antidepressant should not be stopped abruptly due to the risk of withdrawal symptoms, *unless*:

- the drug has caused a serious adverse effect, e.g. a cardiac arrhythmia in association with a tricyclic antidepressant (TCA)
- the patient is entering the terminal phase.

Onset of withdrawal symptoms can occur within a few days, although missing a single dose can precipitate symptoms in susceptible individuals. Problems are more likely with high doses or long courses. Withdrawal symptoms can usually be avoided by tapering the dose of the antidepressant, rather than by abruptly stopping it. Symptoms should not usually last longer than 1–2 weeks. The antidepressant can be restarted if symptoms are severe or prolonged, after which withdrawal symptoms usually resolve within 24 hours. More gradual tapering can then be commenced.

Withdrawal symptoms experienced depend on the type of antidepressant and can vary in form and intensity. For SSRIs, the most common symptoms include flu-like illness, dizziness exacerbated by movement, insomnia, excessive (vivid) dreaming, and irritability. For TCAs, withdrawal symptoms include rebound cholinergic effects such as headache, restlessness, diarrhoea, and nausea or vomiting. Refer to individual monographs in ➔ Chapter 3 for further detail.

In general, when discontinuing an antidepressant, the following should be applied:

- if taken for <8 weeks, dose-taper over 1–2 weeks
- if taken for ≥8 weeks, dose-taper over 4 weeks.

One exception is *fluoxetine*. At a dose of 20mg orally (PO) daily, this may be stopped abruptly because of the long plasma half-life and active metabolite, but at higher doses, gradual withdrawal over 2 weeks is advisable.

Switching antidepressants

Refer to the references if more detailed information is required.

Switching antidepressants can increase the risk of undesirable effects due to the potential for interaction between drugs (e.g. serotonin syndrome, CYP2D6 inhibition); there is also the likelihood of withdrawal symptoms developing due to discontinuation of the first antidepressant.

In the palliative care setting, there may be limited time to achieve an improvement in the mood of the patient, and hence in their quality of life. A more rapid switch under close medical supervision may be indicated.

Before switching antidepressants, several factors must be considered:

- What is the need and urgency for the switch?
- What is the patient's condition?
- What is the current dose of the antidepressant to be withdrawn?

- What is the duration of treatment of the antidepressant to be withdrawn? If ≤8 weeks, it may be possible to shorten the withdrawal period or stop the drug abruptly.
- Is there a risk of serotonin syndrome? (See ➔ Chapter 1, *Serotonin toxicity*, p. 29.)
- Is there a risk of a drug interaction?
- Could the switch result in medication error?

There are several approaches to switching antidepressants that can be considered. Whichever method is used, the patient should be closely monitored.

Method 1: withdrawal and switch

- Involves gradual withdrawal of the first antidepressant over several weeks, followed by initiation (at low doses) of the new antidepressant, with or without a washout period. The duration of the washout period is dependent on the half-life of the drug being discontinued. For example, the elimination half-life of paroxetine is approximately 24 hours; a suitable washout period for paroxetine would be 3–5 days, dependent upon the choice of replacement drug and its susceptibility to CYP2D6 inhibition (i.e. if CYP2D6 inhibition may be a cause for concern, a washout period of 5 days would be more suitable).
- If the first antidepressant has been taken for:
  - ≥8 weeks, dose-taper over 4 weeks
  - <8 weeks, dose-taper over 1–2 weeks.
- Potential risks of administering two antidepressants together include pharmacokinetic interactions (e.g. increased clomipramine levels with paroxetine due to CYP2D6 inhibition) and pharmacodynamic interactions such as serotonin syndrome. This method is suggested for switches where there is a considerable risk of serious drug interaction.
- May not be suitable in palliative care when situations may demand a swifter substitution.
- Switching from fluoxetine requires careful consideration, due to the extended half-life (effects may persist for up to 6 weeks post-discontinuation). Refer to Table 2.11 for advice and further examples.

Method 2: cross-tapering

- The dose of the first antidepressant is gradually reduced, while the dose of the second is introduced at a low initial dose and gradually increased. The speed of cross-tapering may need to be adjusted according to how well the patient tolerates the process.
- Be aware of the possibility of drug interactions when cross-tapering.
- Some drugs should never be co-administered due to the risk of serious drug interactions (see ➔ *Method 1: withdrawal and switch* above) and in these cases, cross-tapering should be avoided.
- Cross-tapering is generally not suitable for fluoxetine due to its long half-life (see ➔ *Method 3: immediate switch* below).

See Table 2.11 for specific examples.

Method 3: immediate switch

- The current antidepressant is stopped abruptly and the new antidepressant is introduced at a low dose, with or without a washout period.
- Useful if switching between two very similar antidepressants, e.g. two SSRIs. The first drug should be discontinued, and the new drug introduced at a low dose.
- Usual method to adopt when swapping from fluoxetine.
- This process may put a patient at greater risk of developing withdrawal symptoms.

See Table 2.11 for specific examples.

Further reading

Bradley N. How do you switch between tricyclic, SSRI and related antidepressants? 2019. Available from: https://www.sps.nhs.uk/articles/how-do-you-switch-between-tricyclic-ssri-and-related-antidepressants/. Accessed 22 July 2021.

Keks N, Hope J, Keogh S. Switching and stopping antidepressants. *Aust Prescr*. 2016;**39**(3):76–83.

Table 2.11 Switching antidepressants

To From	SSRI∞ (except fluoxetine)	Fluoxetine	TCA* (except clomipramine)	Venlafaxine	Duloxetine	Mirtazapine	Trazodone
SSRI∞ (except fluoxetine)	Method 3 Immediate switch	Method 3 Immediate switch	Method 2 Cross-taper cautiously, starting with a low dose of TCA*	Method 3 Immediate switch (although caution if paroxetine involved)	Method 3 Immediate switch (although caution if paroxetine involved)	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously
Fluoxetine 20mg daily§	Method 3 Stop fluoxetine abruptly. Initiate second SSRI at half the normal starting dose 4–7 days later		Method 3 Stop fluoxetine abruptly. Initiate TCA at low dose 4–7 days later; increase dose very slowly	Method 3 Stop fluoxetine abruptly. Initiate venlafaxine 4–7 days later	Method 3 Stop fluoxetine abruptly. Initiate duloxetine 4–7 days later	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously

(Continued)

Table 2.11 *(Contd.)*

To From	SSRI[∞] (except fluoxetine)	Fluoxetine	TCA[*] (except clomipramine)	Venlafaxine	Duloxetine	Mirtazapine	Trazodone
TCA[*] (except clomipramine)	Method 2 Gradually reduce the dose of TCA to 25–50mg daily and then start SSRI at usual dose. Withdraw TCA over next 5–7 days[*]	Method 2 Halve dose of TCA, add fluoxetine, and then slowly withdraw TCA	Method 3 Immediate switch	Method 2 Cross-taper[*] cautiously, starting with low-dose venlafaxine	Method 2 Cross-taper[*] using a low starting dose of duloxetine	Method 2 Cross-taper cautiously	
Venlafaxine	Method 3 Immediate switch (although caution if paroxetine involved)	Method 3 Immediate switch	Method 2 Cross-taper[*] using a low starting dose of TCA		Method 3 Stop venlafaxine. Initiate duloxetine 60mg OD the following day	Method 2 Cross-taper cautiously	
Duloxetine	Method 3 Immediate switch (although caution if paroxetine involved)	Method 3 Immediate switch	Method 2 Cross-taper[*] using a low starting dose of TCA	Method 3 Stop duloxetine. Start venlafaxine at low dose the following day		Method 2 Cross-taper cautiously	

Mirtazapine	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously		Method 2 Cross-taper cautiously
Trazodone	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously with a low dose of TCA	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously	Method 2 Cross-taper cautiously	

[~] Specifically, citalopram, escitalopram, paroxetine, or sertraline.

* See notes on above regarding cross-tapering. Cross-tapering clomipramine with venlafaxine/duloxetine or an SSRI is not recommended.

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

§ Gradual withdrawal over 2 weeks may be necessary at doses >20mg PO OD, rather than stopping abruptly. Note drug interactions (CYP2D6) may persist for up to 5 weeks after discontinuation.

Source: data from *Aust Prescr*. **39**(3), Keks N, Hope J, Keogh S, *Switching and stopping antidepressants*, pp. 76–83, Copyright (2016), NPS MedicineWise; UK Medicines Information (UKMi), *How do you switch between tricyclic, SSRI and related antidepressants?* Copyright (2019), Specialist Pharmacy Service. Available at https://www.sps.nhs.uk/articles/how-do-you-switch-between-tricyclic-ssri-and-related-antidepressants/.

Diabetes in palliative care

Introduction

Diabetes is a relatively common disease in the Western world, with the number of people in the UK diagnosed with diabetes currently estimated at 3.9 million. Most of these cases are of Type 2 diabetes, which has been linked to increasing rates of obesity.

Individuals with Type 2 diabetes typically progress from dietary management to treatment with a single oral agent (usually metformin) to treatment with two or three different agents in combination at intensification steps defined by their glycated haemoglobin (HbA1c). Individuals with Type 1 diabetes, however, have an absolute requirement for insulin treatment, without which they will rapidly become hyperglycaemic and develop diabetic ketoacidosis.

Despite these differences, the aim of diabetes treatment is the same for each patient cohort in palliative care. This is to ensure that the patient maintains effective symptom control while avoiding metabolic decompensation and diabetes-related emergencies. Diabetes UK recommends that this is done by aiming for blood glucose levels between 6 and 15mmol/L.

Management of diabetes—stable disease (1 year + prognosis)

Adjuvant therapies

Cardioprotective therapies (e.g. angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers, aspirin, statins) should be reviewed and dose reduction/drug withdrawal should be considered, taking into account the diagnosis and comorbidities. Patients taking aspirin or long-term steroids may experience increased GI side effects, so should be treated with a PPI or H_2 receptor antagonist for GI protection.

Oral hypoglycaemic agents

Oral hypoglycaemic agents (OHAs) should be reviewed, and target glucose concentrations considered and agreed with the patient. Weight loss may result in a reduced need for OHAs or insulin, so it may offer an opportunity to rationalize treatment.

As appetite reduces, medications that promote satiety (e.g. glucagon-like peptide 1 (GLP-1) receptor agonists, sodium–glucose co-transporter 2 (SGLT2) inhibitors) may no longer be necessary. Equally, if maintaining hydration is an issue, medications that promote diuresis (e.g. SGLT2 inhibitors) may no longer be appropriate. Table 2.12 provides a useful summary of considerations to be made for each OHA.

Insulins

Due to clinical differences between Type 1 and Type 2 diabetes, it is important to identify the patient's Type to provide the best care possible. As appetite and weight fall, the amount of insulin needed to control blood glucose will reduce. A discussion about the likely requirement for dose reduction and alteration of glycaemic targets should be performed early to allow patients and their families to understand that dose reductions are likely. Those with Type 2 diabetes may achieve their revised glycaemic targets

without the use of insulin, but insulin *must not* be stopped in Type 1 diabetes. Patients with Type 1 diabetes may only need basal insulin as dietary intake decreases. Important considerations to be made when reviewing insulin therapies are listed below.

- Doses may need to be changed with changes in renal function, including in those on renal replacement therapy.
- Hypoglycaemia risk will need to be reassessed with changes in eating patterns.
- A change of insulin regimen may be needed to match changes in activity levels.
- Equipment for insulin delivery may need to be reassessed if physical capabilities alter, vision is poor, or carers become involved in giving insulin.
- Evening isophane (Insulatard®/Humulin I®, or Insuman basal®) (cloudy insulin), in combination with daytime oral hypoglycaemic drugs, may be a good first-line treatment choice in individuals with Type 2 diabetes.
- The simplest regimen should be chosen if switching to insulin only; both once- and twice-daily injection can be considered.
- Consider using an analogue basal insulin if the individual is at high risk of hypoglycaemia.
- *Do not stop insulin in individuals with Type 1 diabetes.*

Continuous subcutaneous insulin infusion (insulin pump treatment)

To provide detailed advice about the potential impact of their diagnosis on their diabetes, early involvement of the diabetes specialist nurse should be considered. If, at any time, the individual wishes to stop using their insulin pump, it should be removed 1 hour after a subcutaneous (SUBCUT) dose of basal insulin has been given. Fast-acting insulin should be prescribed as necessary. Important considerations to be made when reviewing insulin pump therapies are listed below.

- A different approach to glucose targets may be appropriate, with an emphasis on safety and avoidance of hypoglycaemia, rather than on achieving tight control.
- A range of basal insulin profiles should be made available in anticipation of changing insulin requirements, e.g. due to weight loss (dose reduction) or corticosteroid treatment (dose increase).
- Mealtime and correction boluses will need to be adjusted to reflect predictable changes in insulin sensitivity and to address the effects of diminishing appetite.

Management of diabetes—unstable/advanced disease (months prognosis)

The aim of treatment is to limit drug interventions to the minimum that controls the patient's symptoms.

- Patients on complex regimens (i.e. multiple OHAs and insulin) should be reviewed, with a view to changing to once- or twice-daily insulin.
- Patients using insulin alone should be reviewed, and their regimen simplified if possible.

Table 2.12 Oral hypoglycaemic agents

Metformin	Sulfonylureas	Pioglitazone	Gliptins	GLP-1 receptor agonists	SGLT2 inhibitors
Risk of hypoglycaemia when used as monotherapy					
No risk	Moderate risk	No risk	Low risk	No risk	High risk
General considerations					
Review dose according to changing renal function	Review if dietary intake is reduced or in the presence of significant weight loss	The risk–benefit ratio for pioglitazone in terminal disease requires review. Pioglitazone should only be prescribed if benefits can be clearly identified	Review doses in accordance with each product's licence as renal function deteriorates	Review if dietary intake is reduced or in the presence of significant weight loss	Refer to individual product SmPC for dosing
Withdraw if creatinine >150mmol/L or eGFR <30mL/min/1.73m^2	Review dose if renal or hepatic function deteriorates and consider switch to tolbutamide		Some gliptins can be used in all stages of renal disease	Withdraw treatment if abdominal pain or pancreatitis develops	Review doses in accordance with each product's licence as renal function deteriorates
Review in presence of gastrointestinal disease or if symptoms of nausea, heartburn, diarrhoea, or flatulence are causing discomfort	Review tolbutamide dose if hepatic function deteriorates as hypoglycaemia may occur	Contraindicated in those with, or at risk of, bladder tumour or heart failure	Co-administration with sulfonylurea increases the risk of hypoglycaemia	Refer to individual product SmPC for dosing	Withdraw treatment if evidence of clinical dehydration, peripheral vascular disease, foot ulceration, or acute illness or pre-surgery Test for ketones in acute illness

GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose co-transporter 2; SmPC, summary of product characteristics; eGFR, estimated glomerular filtration rate.

- If carers are involved in the administration of insulin, treatment should be simplified, where possible, to facilitate easier administration (i.e. OD insulin regimes).
- If changing from twice-daily to OD insulin, the starting dose of long-acting insulin should be lower than the total dose of twice-daily isophane or pre-mixed insulin and 75% of the total previous dose is recommended.

Deterioration (weeks prognosis)

Individuals may present, or be referred, to the diabetes team at this time, in which case all of the suggested changes above should be considered, but keeping in mind that there may be little time to adjust to a new insulin regimen.

Intensive support may be needed for dose adjustments as well-being, activity, and appetite can change day-to-day.

One important consideration is that having to manage diabetes can be an added stress at this emotional time for individuals and carers. Relaxing targets for control may seem like 'giving up' for some, while others may view managing diabetes, in addition to their terminal illness, as 'pointless'.

End-of-life care (days prognosis)

Ideally, by this stage, diabetes treatment has been rationalized, so that few changes are needed in the last days of life. Diabetes UK has developed a useful flow chart on how to manage diabetes in dying individuals (see Fig. 2.2), which aims to minimize symptoms of diabetes while keeping invasive testing to a minimum.

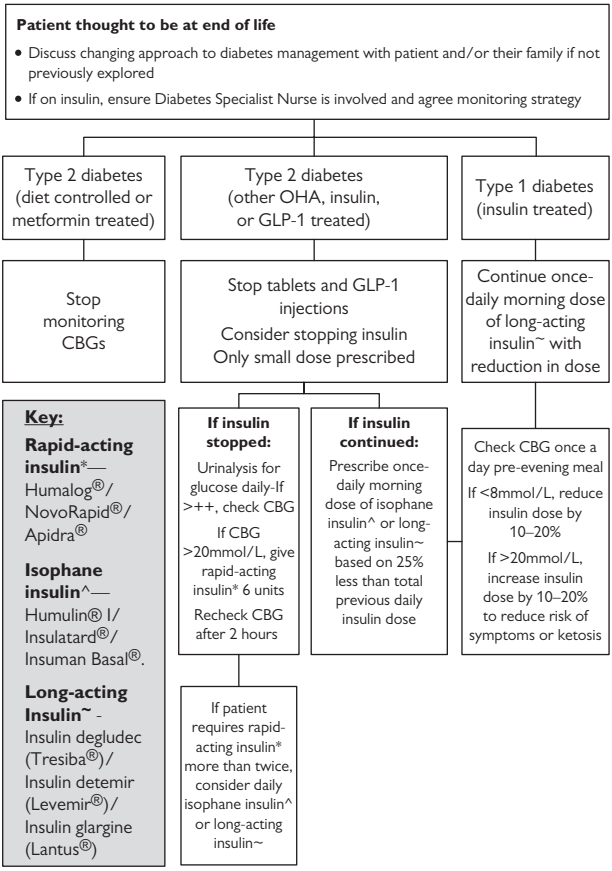
For patients using insulin pump therapy who are no longer able to manage their own pump, it can still be used to deliver their basal insulin requirements if carers have the necessary competencies and support from the relevant team in their chosen place of care.

Management of corticosteroid-induced complications

Corticosteroid therapy is frequently used in palliative care for symptom control, usually as dexamethasone or prednisolone. Treatment may be administered as a single high dose for a defined period and titrated down slowly or used as maintenance therapy for a prolonged period. Treatment may also be given for symptom management at the end of life.

The use of corticosteroid treatment in people with pre-existing diabetes will undoubtedly result in worsening glucose control (corticosteroid-induced hyperglycaemia) and warrants temporary additional and more active glycaemic management. A rise in glucose related to corticosteroid therapy occurring in people without a known diagnosis of diabetes (corticosteroid-induced diabetes) requires monitoring and potential active glycaemic management. Corticosteroid-induced diabetes may or may not resolve when treatment is withdrawn.

Corticosteroids modulate carbohydrate metabolism via several mechanisms, including effects on β-cell function, as well as inducing insulin resistance by effects on insulin receptors in the liver, muscle, and adipose tissue. Factors which place a patient at increased risk of corticosteroid-induced hyperglycaemia or diabetes are shown in Box 2.5.



Key points:

- Keep tests to a minimum. Some testing may be required to ensure unpleasant symptoms do not occur due to low or high blood glucose.
- Symptoms of hypo- or hyperglycaemia are difficult to ascertain in a dying patient.
- If symptoms are observed, abnormal blood glucose levels should be considered.
- Test urine or blood for glucose if the patient is symptomatic.
- Observe for symptoms in patients in whom insulin therapy has been discontinued. Flash glucose monitoring may be useful in these individuals to avoid finger prick testing.

Fig. 2.2 Suggested algorithm for the care of diabetes in the dying individual.

Adapted from Diabetes UK, *End of Life Guidance for Diabetes Care*, Copyright (2021), with permission from The British Diabetic Association. Available at https://diabetes-resources-production.s3.eu-west-1.amazonaws.com/resources-s3/public/2021-11/EoL_TREND_FINAL2_0.pdf

Box 2.5 Predisposing risk factors for corticosteroid-induced hyperglycaemia/diabetes

- Pre-existing Type 1 or Type 2 diabetes
- A family history of Type 2 diabetes
- Previous gestational diabetes
- Previous impaired fasting glucose or impaired glucose tolerance
- Polycystic ovarian disease and/or obesity
- Ethnic minority groups
- History of hyperglycaemia with steroid use

Stable disease (1 year + prognosis)

An HbA1c may be informative prior to initiation of steroids for patients who are thought to be at high risk of steroid-induced diabetes (or those with a current diagnosis of diabetes). Following commencement of corticosteroid treatment, capillary blood glucose (CBG) testing should be initiated at the frequency recommended in Table 2.13.

Table 2.13 Suggested monitoring frequency of capillary blood glucose

No pre-existing diagnosis of diabetes	Pre-existing diagnosis of diabetes
• Monitoring should occur at least once daily (preferably either prior to or 1–2 hours following lunch or evening meal) • If initial CBG <12mmol/L, continue with once-daily CBG testing • If CBG >12mmol/L, increase frequency of testing to FOUR times a day (before meals and bedtime) • If CBG consistently >12mmol/L (i.e. on two occasions within 24 hours), treat as per Fig. 2.3	• Test CBG FOUR times a day (before meals and bedtime), irrespective of prior glycaemic control • If CBG consistently >12mmol/L (i.e. on two occasions within 24 hours), treat as per Fig. 2.4

CBG, capillary blood glucose.

All patients who experience hyperglycaemia as a result of steroid therapy should receive education from an appropriately trained individual, which covers diabetes management, healthy lifestyle choices, and the risk of hypoglycaemia associated with non-insulin and insulin therapies. The aim of any initiated treatment is to control hyperglycaemia to prevent symptoms (fatigue, polyuria, polydipsia) and reduce the risk of acute complications. Figs 2.3 and 2.4 describe the suggested management of steroid-induced diabetes and steroid-induced hyperglycaemia.

Management of steroid-induced diabetes at end of life

The aim of hyperglycaemic monitoring and treatment in patients at the end of life is to minimize symptoms while reducing the burden of invasive monitoring. The management of diabetes at the end of life is discussed earlier in this section (see ➔ *Management of diabetes—unstable/advanced disease (months prognosis)*, p. 81).

Further reading

Diabetes UK. Diabetes prevalence 2019. 2019. Available from: https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2019. Accessed 28 February 2020.

Diabetes UK. End of life guidance for diabetes care (November 2021). 2021. Available from: https://www.diabetes.org.uk/professionals/position-statements-reports/diagnosis-ongoing-management-monitoring/end-of-life-care. Accessed 13 June 2022.

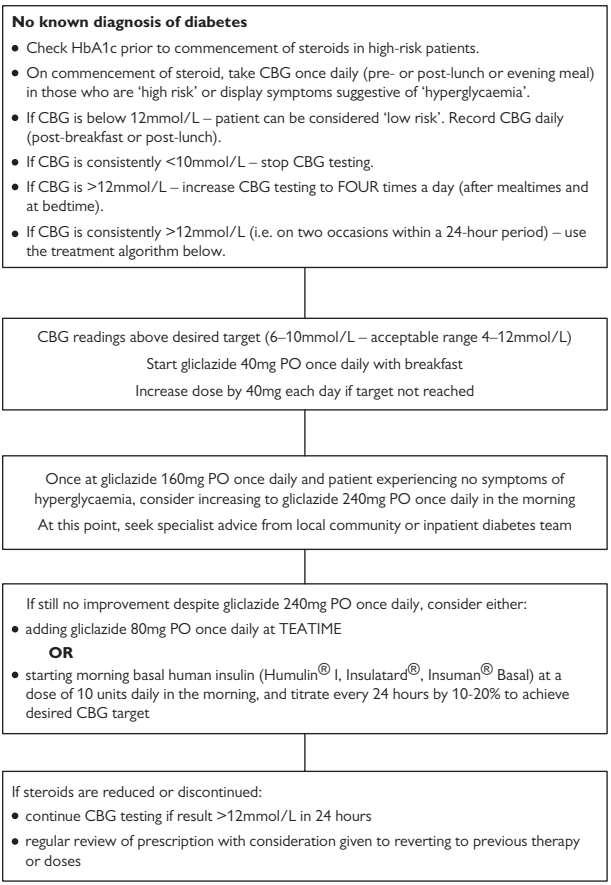


Fig. 2.3 Suggested treatment of steroid-induced diabetes.

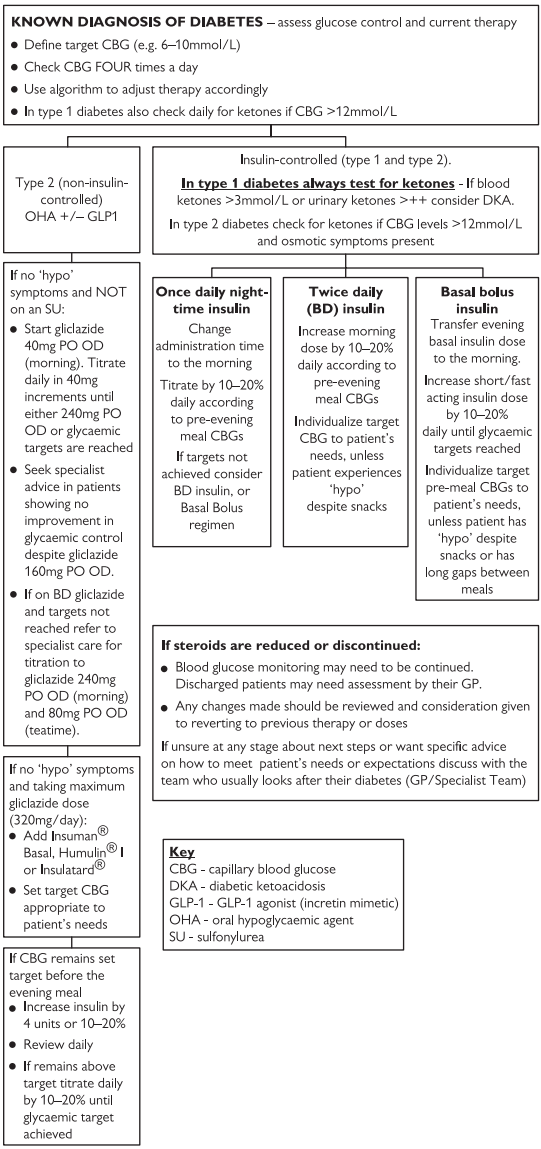


Fig. 2.4 Suggested treatment of steroid-induced hyperglycaemia.

Care of the dying patient

Introduction

- All medication should be reviewed, and non-essential drugs should be deprescribed (see ➔ *Polypharmacy and deprescribing*, p. 71). Unavoidable sudden discontinuation of certain drugs (e.g. antidepressants, baclofen, gabapentin) may lead to the development of withdrawal reactions. These need to be anticipated and treated symptomatically, e.g. with midazolam and/or antiemetics.
- If a patient with Parkinson's disease cannot take medication, sudden withdrawal may lead to a reduction in CNS levels of dopamine, which can lead to a condition that resembles neuroleptic malignant syndrome; it has been termed acute dopamine depletion syndrome. Symptoms include fever, rigidity, autonomic instability, and an altered mental status. Continued treatment at the end of life should be in conjunction with a Parkinson's disease specialist, in order to prevent the development of distressing symptoms. Options include:
  - crushed tablets or liquid medication (dose adjustments may be necessary)
  - inserting a nasogastric tube and converting to products suitable for administration via an enteral feeding tube
  - *rotigotine* patches or SUBCUT/CSCI apomorphine (both can cause agitation and delirium)
  - CSCI *midazolam* ± *hyoscine hydrobromide*.
- In the case of diabetes mellitus, refer to ➔ *Diabetes in palliative care*, p. 80.
- Unless corticosteroids are used for symptom management (e.g. pain, headache, seizures, immunosuppression in the case of transplant patients), it is usually appropriate for them to be withdrawn (tapered if high dose or long duration of treatment).
- Patients with end-stage heart failure should continue to receive medication for as long as possible to prevent distressing symptoms from developing. However, certain treatments can be deprescribed as the patient approaches the end of life. Advice from a cardiology specialist can be helpful. When oral medication is no longer possible, the patient may benefit from *furosemide* via CSCI.
- In many cases, an alternative method of drug administration will invariably be required in order to maintain adequate symptom control as the patient approaches the end of life. The SUBCUT route is usually employed, and most symptoms experienced at the end of life can be adequately controlled with a small number of drugs. Administration via CSCI is a safe, practical, and effective solution.

Anticipatory prescribing

- End-of-life care in community settings will continue to increase in coming years as the population ages and more people die from chronic life-limiting conditions.
- NICE recommends an individualized approach to prescribing of anticipatory medicines for people who may develop symptoms in the last days of life. Anticipatory prescribing is the provision of core

medicines, ahead of possible need, that are essential for the control of symptoms at the end of life. Anticipatory medicines should be prescribed with individualized indications for use, dosage, and route of administration.[1,2] However, there is limited evidence to inform practice, with varied practice across the UK, and there is a risk that prescribing follows inflexible guidelines, rather than allowing an individualized approach. Nonetheless, the practice seeks to allow the patient to remain at home and reduce crisis hospital admissions by permitting timely medication access, e.g. overnight, weekends, or bank holidays.

- Symptoms commonly experienced by patients in the dying phase are:
  - pain
  - nausea and vomiting
  - delirium and terminal restlessness
  - respiratory tract secretions
  - dyspnoea.
- In addition, assessment for the possible risk of the person suddenly deteriorating (e.g. catastrophic haemorrhage, seizures) should occur to ensure anticipatory prescribing of medicines (e.g. *midazolam*) for urgent symptom control.
- Currently, there is no national consensus as to what these medicines should be, but they should comprise:
  - opioid (pain, dyspnoea)
  - antiemetic (nausea and vomiting)
  - sedative (delirium and terminal restlessness)
  - anticholinergic (respiratory tract secretions).
- Anticipatory medicines are prescribed on a PRN basis, rather than as regular administration via CSCI. The Association of Supportive and Palliative Care Pharmacy (ASPCP) recently issued a statement recommending against anticipatory prescribing of a CSCI due to the potential risks[3] of:
  - lack of individualization of care
  - no anticipation of dose/drug changes between prescribing and initiation
  - medication errors—potentially due to timing of the CSCI relative to previous treatment.
- Anticipatory prescribing of a CSCI should only occur if there are robust governance and documentation systems in place to support such practice.
- Examples of drugs and doses that may be considered for anticipatory prescribing are shown below:
  - *morphine* (pain) 2.5mg to 5mg SUBCUT 2- to 4-hourly PRN (hourly under specialist supervision)
  - *levomepromazine* (nausea) 2.5mg to 5mg SUBCUT 4-hourly PRN
  - *midazolam* (agitation) 2.5mg to 5mg SUBCUT 4-hourly PRN (hourly under specialist supervision)
  - *glycopyrronium* (secretions) 200 micrograms SUBCUT 4-hourly PRN.

Managing pain

- *Morphine* is generally considered the first-line opioid for SUBCUT administration at the end of life, unless the patient is already established

on an alternative opioid. Initial doses depend upon current opioid requirements.

- A suitable dose of *morphine* for an opioid-naïve patient for anticipatory prescribing would be 2.5mg to 5mg SUBCUT 2- to 4-hourly PRN. Lower doses may be considered for the frail or elderly. Under specialist supervision, PRN doses may be given as frequently as every hour. After assessment, a CSCI can be considered if several rescue doses have been required in a 24-hour period.
- *Diamorphine* used to be considered the opioid of choice for SUBCUT administration. It is more soluble than morphine, but more expensive. As such, its use should generally be reserved for patients with high opioid dose requirements (e.g. >300mg SUBCUT morphine in 24 hours).
- Patients established on a regular dose of oral opioid should be converted to an appropriate dose for CSCI (see ➔ *Equianalgesia and opioid switch*, p. 56). Examples are shown below.

PO morphine to SUBCUT morphine (2:1):

- Divide the total daily dose of PO morphine by 2 to give the equivalent daily dose of SUBCUT morphine.
- For example, morphine modified-release 90mg PO twice daily (BD) = 180mg PO morphine daily = 90mg SUBCUT morphine daily.

PO oxycodone to SUBCUT oxycodone (1.5:1):

- Divide the total daily dose of PO oxycodone by 1.5 to give the equivalent daily dose of SUBCUT oxycodone (*NB—the manufacturer states to divide by 2*).
- For example, oxycodone modified-release 45mg PO BD = 90mg PO oxycodone daily = 60mg SUBCUT oxycodone daily.
- If a patient has been using oral *methadone* and a CSCI is required, halve the oral dose, although some patients may require a fairly rapid dose escalation, as for some, the ratio approaches 1:1. Refer to the monograph in ➔ Chapter 3 for more details.
- Should it be necessary to change to an alternative opioid, initial dose conversions should be conservative because equianalgesic doses are difficult to determine in practice due to wide interpatient variation. Refer to ➔ *Equianalgesia and opioid switch*, p. 56 above for conversion between opioids.
- A suggested management plan for pain at the end of life is summarized in Fig. 2.5.
- In patients with renal impairment, use of *alfentanil* or *fentanyl* via a CSCI may be appropriate.
- If a patient is receiving analgesic treatment with a transdermal patch (i.e. *buprenorphine* or *fentanyl*), this should remain *in situ*, with further analgesic requirements being administered using rescue doses of SUBCUT morphine (or alternative) and subsequent CSCI. Suitable rescue doses for transdermal buprenorphine and fentanyl patches are shown in Tables 2.14 and 2.15, respectively.
- BTcP should be managed as described in see ➔ *Breakthrough cancer pain*, p. 54. Products currently available can be used successfully during end-of-life care.

- Unresolved pain can present problems during end-of-life care. The vast majority of adjuvant analgesics cannot be administered SUBCUT. Some of the adjuvants, such as TCAs, have a relatively long half-life, so their actions may persist for several days after discontinuation. Drugs such as *clonazepam*, *ketamine*, *ketorolac*, or *parecoxib* can be administered via a CSCI and may be considered for the treatment of unresolved pain.

Table 2.14 Determination of subcutaneous rescue doses of morphine and oxycodone for patients using a transdermal buprenorphine patch

Buprenorphine patch strength (micrograms/hour)	Morphine or oxycodone subcutaneous rescue dose (mg)*
10	2.5
20	5
35	5 to 10
52.5	10
70	10 to 15
105	15 to 25
140	20 to 30

* Based on a conversion of 1:1 between subcutaneous morphine and oxycodone (see *Equianalgesia and opioid switch*, p. 56).

Table 2.15 Determination of subcutaneous rescue doses of morphine and oxycodone for patients using a transdermal fentanyl patch

Fentanyl patch strength (micrograms/hour)	Morphine or oxycodone subcutaneous rescue dose (mg)*
12	2.5
25	5
50	10
75	15
100	20

* Based on a conversion of 1:1 between subcutaneous morphine and oxycodone (see *Equianalgesia and opioid switch*, p. 56).

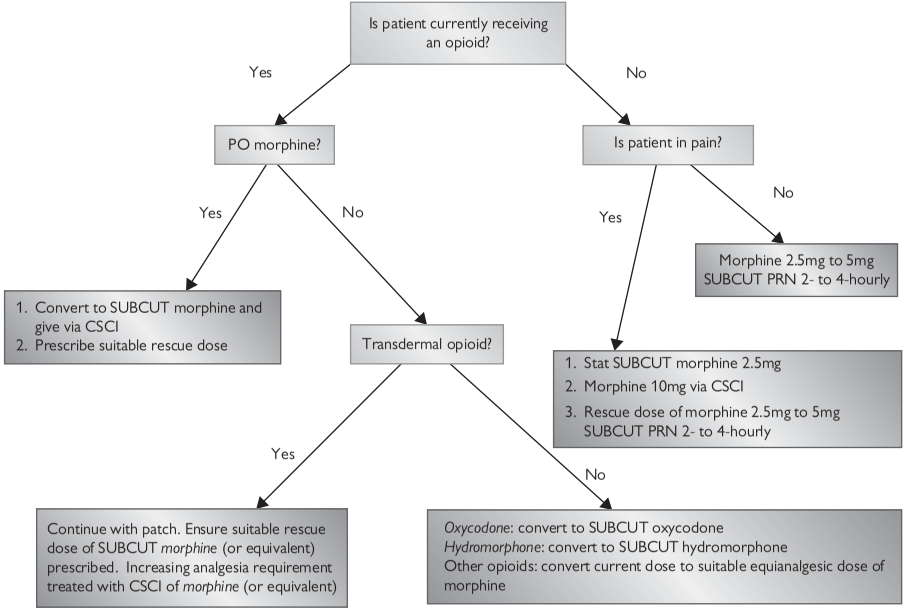


Fig. 2.5 Suggested management of pain with opioids at the end of life.

Managing nausea and vomiting

- It would be prudent to select a drug that has a broad spectrum of action in this scenario. *Levomepromazine* 2.5mg to 5mg SUBCUT four times daily (QDS) PRN would be a suitable choice. Alternatively, *cyclizine* 50mg SUBCUT three times daily (TDS) PRN may be considered. Note that cyclizine can exacerbate congestive heart failure and should be avoided in patients with such. *Haloperidol* 0.5mg TDS SUBCUT PRN may be considered if any nausea and vomiting is expected to be drug-induced. In all cases, after assessment, a CSCI may be considered.
- If large volumes are being vomited, use of anti-secretory drugs such as *octreotide* 500 micrograms ± *glycopyrronium* 1.2mg (or *hyoscine butylbromide* 120mg) via CSCI over 24 hours can be considered.
- The 5-HT_3 antagonists (e.g. *granisetron, ondansetron*) are suitable second-line choices if the cause of nausea and vomiting is due to renal failure or damage to GI enterochromaffin cells, i.e. recent radiotherapy/chemotherapy, bowel obstruction, or gastric cancers.
- *Dexamethasone* can be used in resistant cases and often produces an indirect antiemetic effect, particularly in bowel obstruction.
- *Ranitidine* via CSCI has been used in the management of bowel obstruction (to reduce gastric secretions) and to treat dyspepsia. (NB—refer to the monograph in ➔ Chapter 3.)

Managing delirium and terminal restlessness

- Delirium is one of the most common neurological problems experienced with advanced or end-stage disease.
- The underlying aetiologies are numerous and include CNS malignancy, drug adverse effects, infection, liver/renal impairment, and metabolic abnormalities.
- The diagnosis of delirium is made using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria. All of the following symptoms should be present:
  - disturbance of consciousness (e.g. reduced ability to maintain focus, or shift attention)
  - altered cognition that represents a change from the patient's usual state such as memory deficit or disorientation
  - condition that develops abruptly (usually hours to days) and can fluctuate throughout the day
  - disturbance related to a medical condition.
- There are three clinical subtypes of delirium:
  - hypoactive—characterized by fatigue, lethargy, and sedation; often mistaken for depression or drug adverse effects
  - hyperactive—characterized by restlessness, agitation, myoclonus, hallucinations, and delusions; can be mistaken for uncontrolled pain
  - mixed.
- Hypoactive delirium is believed to be the more common subtype and is associated with a greater mortality rate.
- Delirium may be a reversible condition (e.g. nicotine withdrawal), or it can signal an irreversible deterioration due to disease progression.
- Numerous 'reversible' precipitating factors have been identified and include:

  - hypoxia, metabolic disturbances, and anticholinergic medications (hypoactive)
  - alcohol and drug withdrawal, drug intoxication, or medication adverse effects (hyperactive).
- Agitation and delirium contribute to the condition known as 'terminal restlessness'. Treatment of terminal restlessness is defined by the symptoms displayed.
- Reversible causes should be corrected where possible or appropriate:
  - alcohol/nicotine withdrawal
  - biochemical abnormalities (e.g. hypercalcaemia, hypoglycaemia)
  - brain tumour/metastases
  - constipation
  - drugs (e.g. as renal/liver function deteriorates)
  - emotional distress (e.g. fear, anxiety)
  - infection
  - pain
  - urinary retention.
- Non-pharmacological measures may be useful and include a quiet room and avoidance of isolation or loneliness.
- Benzodiazepines are considered the first-line choice for management of agitation. Note that they can exacerbate symptoms associated with delirium. If the patient shows signs of delirium (e.g. paranoia, hallucinations, altered cognition), an antipsychotic may be a more appropriate first-line treatment.

Agitation

1. Begin with *midazolam* 2.5mg to 5mg SUBCUT 4-hourly PRN (hourly under specialist supervision).
2. If several PRN doses are administered in a 24-hour period, consider adding to, or commencing, a CSCI. A suitable dose would be 10mg via CSCI over 24 hours. Continue to administer appropriate PRN doses and review requirements daily.
3. The dose can be increased as necessary, up to an arbitrary dose of 30mg of midazolam via CSCI over 24 hours. Further dose increases should only occur after thorough assessment.
4. If there is only partial response to the benzodiazepine, consider adding *levomepromazine* 25mg to the CSCI (check for compatibility). Increase the dose as necessary in 25mg to 50mg increments up to a maximum of 200mg over 24 hours. It is a useful adjunct to a benzodiazepine for uncontrolled agitation.
5. In refractory cases, *phenobarbital* may be used for the management of agitation at the end of life.

Delirium

1. Begin *haloperidol* 0.5mg to 2mg SUBCUT every 4 hours PRN (may be given more frequently in specialist centres).
2. Consider adding to, or commencing, a CSCI if several PRN doses are administered in a 24-hour period. A suitable starting dose would be 2.5mg via CSCI over 24 hours. Increase the dose as necessary up to a maximum of 10mg over 24 hours.

3. If no or partial response, *levomepromazine* as detailed earlier may be used in place of haloperidol.
4. In rare instances, *olanzapine* has been administered via CSCI.
5. In refractory cases, *phenobarbital* may be used.

Managing respiratory tract secretions

- Management of respiratory tract secretions in the dying patient is, in most cases, primarily aimed at minimizing the distress of relatives or carers, rather than of the patient. Excess respiratory tract secretions are unlikely to cause pain or distress to the patient.
- Non-pharmacological measures are an important part of the management of respiratory tract secretions and may include repositioning the patient and suction (rarely).
- The main treatment of terminal secretions involves the use of anticholinergic drugs (see monographs in ➔ Chapter 3 for more details):
  - *hyoscine butylbromide* 20mg SUBCUT hourly PRN
  - *glycopyrronium* 200 micrograms SUBCUT 4-hourly PRN
  - *hyoscine hydrobromide* 400 micrograms SUBCUT hourly PRN.
- There is no evidence to support the superiority of any one drug.
- If the patient is no longer able to clear secretions by coughing, a PRN dose should be administered as soon as practical. Anticholinergic drugs do not relieve symptoms from secretions already present. Regular administration or a CSCI should be started as soon as possible.

Managing dyspnoea

- The aim of treatment is to reduce the level of anxiety and alter the perception of breathlessness, ensuring the patient remains comfortable.
- Non-pharmacological measures, such as a fan passing cool air over the face, are important and should not be overlooked.
- Terminal secretions may contribute to the development of terminal dyspnoea and should be treated as described earlier.
- Pharmacological treatment can involve:
  - *Morphine* 1.25mg to 2.5mg SUBCUT 2- to 4-hourly PRN (hourly under specialist supervision) for opioid-naïve patients. For patients established on opioids, use PRN doses initially based on one-sixth of the background dose and amend, as necessary. If several PRN doses are administered in a 24-hour period, consider adding to, or commencing, a CSCI (suitable starting dose for opioid-naïve patients 5mg to 10mg via CSCI over 24 hours).
  - Addition of *midazolam* 2.5mg to 5mg SUBCUT 4-hourly PRN (hourly under specialist supervision). If several PRN doses are administered in a 24-hour period, consider adding to, or commencing, a CSCI (suitable starting dose 10mg via CSCI over 24 hours).
  - Other options include *levomepromazine*, *promethazine*, and *furosemide* (associated with end-stage heart failure). The evidence for these is weaker.

References and further reading

1. National Institute for Health and Care Excellence. Care of dying adults in the last days of life. NICE guideline [NG31]. 2015. Available from: https://www.nice.org.uk/guidance/ng31. Accessed 22 February 2021.
2. National Institute for Health and Care Excellence. Care of dying adults in the last days of life. Quality standard [QS144]. 2017. Available from: https://www.nice.org.uk/guidance/qs144. Accessed 22 February 2021.
3. Association of Supportive and Palliative Care Pharmacy (ASPCP). Anticipatory prescribing of medicines for syringe pumps—ASPCP policy statement. 2020. Available from: https://www.aspcp.uk/anticipatory-prescribing-of-medicines-for-syringe-pumps-aspcp-policy-statement/. Accessed 10 April 2021.

Chapter 3

Monographs A–Z

Monographs

The monographs are divided into numerous sections as described below. The layout has been designed to provide the healthcare professional with quick access to useful, practical, and relevant information. If more in-depth pharmacological information is required, other reference sources should be consulted.

Note the monographs refer to drugs currently available to prescribe in the UK.

Products available

- Information about the brand(s) and generic formulations (where applicable), including legal category, available strengths, and quantity of tablets, capsules, etc. per original pack (where available).
- The legal classification of medicines is shown in ➔ Chapter 2, *Legal categories of medicine*, p. 37.

Indications

- Lists the indications for which the drug is used in palliative care. This can include both licensed and unlicensed uses; the latter are clearly marked with a symbol (+). Note that unlicensed uses may only relate to case reports, and inclusion here does not constitute a recommendation to prescribe. Readers should also refer to ➔ Chapter 2, *Unlicensed use of medicines*, p. 36 for information on the use of licensed drugs for unlicensed purposes.

Contraindications and cautions

- A selection of contraindications and cautions are presented here. The reader should refer to the product's summary of product characteristics (SmPC) for a complete list. Note that it is assumed that hypersensitivity to the drug is a contraindication and is not included in each monograph.

Adverse effects

- Describes a selection of undesirable effects that have been reported.
- The monographs classify undesirable effects as per the SmPC:
  - very common (≥10%)
  - common (≥1%, <10%)
  - uncommon (≥0.1%, <1%)
  - rare (≥0.01%, <0.1%)
  - very rare (<0.01%)
  - unknown.
- Certain SmPCs have not been updated and do not use this system. In such cases, the frequency of undesirable effects as described in the SmPC has been included.
- The reader is referred to the SmPC for a complete list.

Drug interactions

- Provides a list of potential and actual pharmacokinetic and pharmacodynamic drug interactions. The reader should read ➔ Chapter 1, *Drug interactions*, p. 25 in order to fully appreciate this section. Information relating to cytochrome involvement is provided, as this information can be used to anticipate or identify drug interactions. The

Cytochrome P450 tables on the inside back cover provide a quick reference guide to cytochrome substrates, inducers, and inhibitors. Be aware that some drugs are metabolized by multiple cytochrome pathways, and while one drug interaction may seem unimportant, if additional drugs are co-prescribed that affect other metabolic pathways, this interaction may assume greater significance. Note that while the qualitative nature of a drug interaction can be predicted from pharmacology, the quantitative nature (i.e. clinical significance) is, in many cases, difficult to predict.

Dose

- Information for each indication described in *Indications* is provided. Unlicensed indications are shown by the symbol (+).

Dose adjustments

- A quick guide to dosage adjustments that may be required in the elderly or in those with hepatic/renal impairment. For complete information, the reader is referred to the SmPC.

Additional information

- Further relevant information about the practical use of the drug is found here.
- Although brief information on continuous subcutaneous infusion (CSCI) stability is also provided here, this does not indicate stability for all ranges of concentrations. For more detailed information, the reader is referred to Dickman A and Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Pharmacology

- A synopsis of the pharmacology is included in the monograph.

Alfentanil ⚠

Rapifen® (CD2 POM)
Injection: 500 micrograms/mL (10 × 2mL; 10 × 10mL).

Rapifen Intensive Care® (CD2 POM)
Injection: 5mg/mL (10 × 1mL).

Generic (CD2 POM)
Injection: 500 micrograms/mL (10 × 2mL; 10 × 10mL); 5mg/mL (5; 10).

Unlicensed special (CD2 POM)
Nasal spray: 5mg/5mL (5mL; each actuation delivers 0.14mg in 0.14mL; attachment supplied for sublingual or buccal administration); see ➔ *Additional information*, p. 105 for supply issues.

Indications

- ⁺Alternative analgesic for SUBCUT administration, especially in renal failure.[1]
- ⁺Management of BTcP. Refer to ➔ Chapter 2, *Breakthrough cancer pain*, p. 54 for guidance relating to BTcP.[2]

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care. There may, however, be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation).
- Concurrent administration with MAOIs, or within 2 weeks of their discontinuation, is contraindicated (risk of serotonin toxicity; see ➔ Chapter 1, *Serotonin toxicity*, p. 29). If concomitant use is unavoidable (e.g. linezolid), ensure there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 25). Of the opioids, morphine is believed to carry the lowest risk. Alfentanil is also believed to carry a low risk; nonetheless, treatment must be reviewed urgently if symptoms develop, alfentanil should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with clonazepam and methadone among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[3] The SmPC warns that concurrent use of alfentanil and benzodiazepines (or zopiclone/zolpidem) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression

and sedation. Patients (and carers) should be made aware of these symptoms.
- May cause hypotension; use caution if the patient is ambulatory.
- Empirical dose adjustment may be necessary in hepatic impairment (see ➔ *Dose adjustments*, p. 104).
- Metabolism of alfentanil involves CYP3A4 and is susceptible to drug interactions (see ➔ *Drug interactions*, p. 102).
- Alfentanil may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for more information.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid. This is termed opioid-induced hyperalgesia (OIH). Pain associated with OIH tends to be more diffuse than pre-existing pain and less defined in quality. The risk of developing OIH depends not only on the dose of opioid taken, but also on factors such as gender, age, genotype, and cause of pain, i.e. each case will be unique. Management of OIH can involve changing the opioid, reduction in the dose (by 25–50%), and addition of non-opioid analgesics such as ketamine or pregabalin/gabapentin.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. Strong opioids tend to cause similar adverse effects, albeit to varying degrees.
- *Very common*: constipation*, nausea, vomiting.
- *Common*: bradycardia, drowsiness, postural hypotension.
- *Uncommon*: headache, pruritus.
- *Rare*: respiratory depression.
- *Unknown*: irritation/local reaction (nasal spray/CSCI).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Alfentanil is metabolized by CYP3A4 and CYP3A5. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of,

* Given the licensed indication of alfentanil, constipation is not specifically mentioned in the SmPC. Nonetheless, as with all opioids, continued use is expected to result in constipation.

this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Aprepitant*—with acute treatment, aprepitant can enhance the effect of alfentanil (moderate CYP3A4 inhibition—greater effect on orally administered drugs); within 3–5 days of completing a 3-day course of aprepitant, the effect of alfentanil may be reduced (mild CYP3A4 induction).
- *Clarithromycin*—may enhance effect of alfentanil; dose reduction may be necessary.
- *Carbamazepine*—may reduce the efficacy of alfentanil.
- *Dexamethasone*—high dose (e.g. 12mg to 16mg PO OD) may reduce the efficacy of alfentanil.
- *Enzalutamide*—may reduce the efficacy of alfentanil.
- *Erythromycin*—may enhance the effect of alfentanil; dose reduction may be necessary.
- *Fluconazole*—may inhibit the metabolism of alfentanil (although more likely to occur when fluconazole doses are >200mg daily).
- *Midazolam*—effect may be enhanced by alfentanil (competitive inhibition of metabolism).
- *Phenobarbital*—may reduce the efficacy of alfentanil.
- *Phenytoin*—may reduce the efficacy of alfentanil.
- *Rifampicin*—can reduce the efficacy of alfentanil.

Pharmacodynamic
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see *Contraindications and cautions*, p. 101.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing effect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine; the prescriber should be aware of the need to reduce the opioid dose.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOI*—risk of severe and unpredictable interactions with MAOIs, involving potentiation of opioid or serotonergic effects.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see *Contraindications and cautions*, p. 101.

Dose

The initial dose of alfentanil depends upon the patient's previous opioid requirements. Refer to Chapter 2, *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences. Note the wide variability when converting to or from alfentanil. Values quoted for the equianalgesic ratio of diamorphine:alfentanil vary from 1:10 to 1:6.[4] Use of the 10:1 ratio is recommended when rotating from diamorphine to alfentanil; when rotating from alfentanil to diamorphine, use of the 1:6 ratio is recommended.

+Pain

- For opioid-naïve patients, typical starting dose of 0.5mg to 1mg by CSCI over 24 hours.
- Given the short duration of action of alfentanil (<30 minutes), it is unusual to titrate background pain with PRN doses of this opioid. Typically, an equivalent dose of alternative opioid (e.g. oxycodone) is used, based on one-sixth to one-tenth of the 24-hour alfentanil requirements. Note that it may be necessary to make empirical dose adjustments of the alternative opioid in renal impairment. For example, consider alfentanil 3mg via CSCI:
  - normal renal function, use oxycodone 5mg to 10mg SUBCUT PRN every 1 to 2 hours
  - impaired renal function, use oxycodone 2.5mg to 5mg SUBCUT PRN every 3 to 4 hours.
- Note that the European Association for Palliative Care (EAPC) evidence-based recommendations suggest that for patients with renal impairment (GFR <30mL/min), the opioid of first choice should be fentanyl or buprenorphine administered SUBCUT (or IV).[5]
- For pain precipitated by a procedure, such as dressing changes or personal care, an appropriate SUBCUT dose based on *one-sixth* to *one-tenth* of the 24-hour opioid dose can be helpful. This should be administered 5–10 minutes prior to the procedure.

+Breakthrough cancer pain

- There is no correlation between the dose of opioid used for persistent background pain and the dose needed to treat BTcP.
- Note that several fentanyl products are licensed to treat BTcp and should be used in preference to alfentanil.
- The patient must be using opioids for persistent background pain (at a daily dose equivalent to 60mg PO morphine).
- No validated treatment schedule exists. A suggested starting dose is 140micrograms to 280 micrograms using the nasal spray (equivalent to 1–2 sprays), increased as necessary.
- The prescriber should consider any coexisting oral or nasal condition before using the nasal spray.
- The background dose should not need adjusting if alfentanil is used to treat BTcP.

Dose adjustments

Elderly

- No specific guidance is available. Dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance is available.
- In hepatic impairment, the half-life and free fraction of alfentanil increase. An empirical dose reduction may be necessary as the effect can be more prolonged and pronounced. This is of importance if changing from another opioid using conventional equianalgesic values.

- Alfentanil is one of the drugs of choice in renal disease. Although the clearance is unaltered, the free fraction of alfentanil is raised in renal impairment. Dose requirements should be individually titrated.

Additional information

- If other analgesic measures are introduced—pharmacological or other alternatives, e.g. radiotherapy—the dose of alfentanil may need to be reduced.
- Alfentanil spray is available from the manufacturing unit at Torbay Hospital. Delivery can take up to 5 working days (Tel: 01803 664707; Fax: 01803 664354). The product remains stable for 28 days once opened.
- Alfentanil is reportedly chemically and physically compatible under stated conditions with cyclizine (*NB—there is a possible concentration-dependent compatibility issue with cyclizine, similar to that seen with diamorphine*), haloperidol, metoclopramide, midazolam, and ondansetron. Under stated conditions, alfentanil is physically compatible with clonazepam, dexamethasone, glycopyrronium, hyoscine butylbromide, levomepromazine, and octreotide.[5]

Pharmacology

Alfentanil is a synthetic opioid, chemically related to fentanyl, and is more lipophilic than morphine. It is a suitable alternative to morphine for use in a CSCI, particularly in patients with renal failure. Alfentanil is approximately ten times as potent as diamorphine (given SUBCUT). It is extensively metabolized in the liver by CYP3A4/5 enzymes to inactive compounds. Drugs that inhibit or induce CYP3A4/5 could alter responses to alfentanil. Note that although patients requiring a CSCI of alfentanil are unlikely to be using most of these drugs, their effect on alfentanil metabolism may persist for several days, even after cessation. The CYP3A5 phenotype (usually inactive in the majority of Caucasians) may explain unexpected poor responses (see Box 1.3).

References and further reading

1. Sande TA, Laird BJ, Fallon MT. The use of opioids in cancer patients with renal impairment-a systematic review. *Support Care Cancer*. 2017;**25**(2):661–75.
2. Duncan A. The use of fentanyl and alfentanil sprays for episodic pain. *Palliat Med*. 2002;**16**(6):550.
3. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
4. Cran A, Dorman S, Kirkham S. Opioid rotation to alfentanil: comparative evaluation of conversion ratios. *BMJ Support Palliat Care*. 2017;**7**(3):265–6.
5. Caraceni A, Hanks G, Kaasa S, *et al*. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;**13**(2):e58–68.
Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Allopurinol

Zyloric® (POM)

Tablet: 100mg (28; 100); 300mg (28).

Generic (POM)

Tablet: 100mg (28; 100); 300mg (28).

Unlicensed (POM)

Oral suspension: 100mg/5mL (150mL).

Indications

- Prophylaxis of:
  - gout
  - hyperuricaemia associated with cancer chemotherapy
  - renal stones.

Contraindications and cautions

- Allopurinol should be withdrawn immediately if a skin rash or other evidence of sensitivity occurs, as this could result in more serious hypersensitivity reactions (see ➔ *Adverse effects*).
  - The HLA-B*58:01 allele is found in up to 20–30% of people from Han Chinese, African, and Indian ancestry, and is associated with an increased risk of allopurinol-induced skin toxicity. Screening is suggested in these populations prior to commencing allopurinol.
  - Patients with chronic renal impairment and concurrent use of diuretics (especially thiazides) may be at greater risk of developing serious skin reactions.
- Allopurinol treatment should not be started until an acute attack of gout has completely resolved.
- Acute attacks of gout may be precipitated during allopurinol use. It is advisable to give prophylaxis treatment during early treatment (e.g. until 1 month after hyperuricaemia has been corrected) with an NSAID or colchicine. Allopurinol need not be discontinued.
- Patients should be adequately hydrated to prevent xanthine deposition in the urinary tract (of particular importance during chemotherapy).
- May cause an increase in TSH with chronic treatment.
- Use with caution in patients with hepatic and renal impairment (see ➔ *Dose adjustments*, p. 107).

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: rash (withdraw treatment; can reintroduce gradually if mild, but withdraw permanently if recurs).
- *Uncommon*: altered LFTs, hypersensitivity reactions*, nausea/vomiting (can be avoided by taking after meals).

* A delayed hypersensitivity disorder, known as hypersensitivity syndrome (HSS) or drug reaction with eosinophilia and systemic symptoms (DRESS), may occur at any time during treatment, with

- *Rare*: hepatitis, Stevens–Johnson syndrome/toxic epidermal necrolysis (usually within first few weeks of treatment).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized by xanthine oxidase (the cytochrome P450 system is not involved).
- *Aluminium hydroxide*—may reduce the effectiveness of allopurinol; an interval of at least 3 hours between drugs.
- *Aspirin/salicylates*—may reduce the effectiveness of allopurinol.
- *Azathioprine/6-mercaptopurine*—azathioprine is a pro-drug of 6-mercaptopurine; allopurinol inhibits the metabolism of 6-mercaptopurine; doses of both azathioprine and 6-mercaptopurine should be reduced by 75%.
- *Ciclosporin*—plasma concentration of ciclosporin may increase.
- *Theophylline*—plasma concentration of theophylline may increase.

Pharmacodynamic

- *ACE-Is*—possible increase in risk of hypersensitivity reactions.
- *Amoxicillin/ampicillin*—possible increase in risk of skin reactions.
- *Diuretics*—increased risk of severe hypersensitivity skin reactions, especially in renal impairment.

Dose

- Initial dose 100mg PO OD after food.
- Usual maintenance dose:
  - 100mg to 200mg PO daily (mild conditions)
  - 300mg to 600mg PO daily (moderate conditions)
  - 700mg to 900mg PO daily (severe conditions).
- Doses of over 300mg are given in two or more divided doses (to reduce GI intolerance).

Dose adjustments

Elderly

- The lowest effective dose should be used.

Hepatic/renal impairment

- In hepatic impairment, the manufacturer advises that reduced doses should be used. Periodic LFTs should be performed.
- In mild to moderate renal impairment, a maximum dose of 100mg PO OD is recommended and should only be increased if response is inadequate. In severe renal impairment, doses should not exceed 100mg PO OD, or the dosing interval should be increased.

symptoms such as abnormal LFTs, arthralgia, fever, rashes, and vasculitis. Initial symptoms may resemble an acute viral infection. Acute anaphylactic shock has been reported. If such reactions do occur, allopurinol should be withdrawn immediately and permanently.

- Allopurinol and its metabolites are removed by renal dialysis. If dialysis is required 2–3 times a week, consideration should be given to an alternative dosage schedule of 300mg to 400mg allopurinol immediately after each dialysis, with none in the interim.

Additional information

- Tablets can be dispersed in water immediately prior to administration if necessary.

Pharmacology

Allopurinol (and its main metabolite oxipurinol) inhibits the enzyme xanthine oxidase, blocking the conversion of hypoxanthine and xanthine to uric acid. It is rapidly absorbed from the upper GI tract, with a bioavailability of 67–90%. The majority of a dose is eliminated through metabolism; <10% is excreted unchanged.

Amitriptyline ♡

Generic (POM)
Tablet: 10mg (28); 25mg (28); 50mg (28).
Oral solution: 10mg/5mL (150mL); 25mg/5mL (150mL); 50mg/5mL (150mL).

Indications

- Depression.
- Migraine/chronic tension-type headache.
- Neuropathic pain.[1]

Contraindications and cautions

- Amitriptyline is contraindicated for use in the following:
  - arrhythmias
  - mania
  - porphyria
  - recent myocardial infarction
  - severe liver disease.
- Do not use with an irreversible MAOI, or within 14 days of stopping one, or at least 24 hours after discontinuation of a reversible MAOI (e.g. *moclobemide*, *linezolid*). Note that in exceptional circumstances, *linezolid* may be given with amitriptyline, but the patient must be closely monitored for symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- There is a *conditional* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 111)
  - avoid concomitant administration of drugs that impair elimination (see ➔ *Drug interactions*, p. 111)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct significant electrolyte disturbances (e.g. hypokalaemia or hypomagnesaemia) before commencing treatment.
- The SmPC makes a specific recommendation about CYP2C19 and CYP2D6 poor metabolizers (see ➔ *Dose*, p. 112). Note that development of adverse effects is not a predictor of genetic status.
- Dose reduction should be considered if a strong CYP2D6 or CYP2C19 inhibitor is added to treatment (see ➔ *Drug interactions*, p. 101).
- There is a risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when amitriptyline is used concomitantly with certain drugs. Treatment should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Amitriptyline should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 111).
- Use with caution in epilepsy (may lower seizure threshold). *SSRIs* are considered to be antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.
- In addition, amitriptyline should be used with caution in patients with:

  - CV disorders
  - diabetes (may alter glycaemic control)
  - hepatic impairment
  - hyperthyroid patients or those receiving thyroid medication (enhances the response to antidepressants)
  - narrow-angle glaucoma
  - prostatic hypertrophy
  - urinary retention.
- Elderly patients are more susceptible to adverse effects (see ➔ *Dose adjustments*, p. 112). Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs, without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- There is an increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs. The mechanism is unknown.
- Avoid abrupt withdrawal, as symptoms such as nausea, headache, and malaise can occur. Although generally mild, they can be severe in some patients. Withdrawal symptoms usually occur within the first few days of discontinuing treatment and they usually resolve within 2 weeks, though they can persist in some patients for up to 3 months or longer. See ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants. If withdrawal symptoms emerge during discontinuation, raise the dose to stop symptoms and then restart withdrawal much more gradually.
- Amitriptyline may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: accommodation disorder; aggression; congested nose; constipation; dizziness; drowsiness; dry mouth; headache; hyperhidrosis; nausea; palpitations; speech disorder (dysarthria); tachycardia; tremor; weight increase.
- *Common*: agitation; ataxia; atrioventricular block; confusional state; dysgeusia; erectile dysfunction; hyponatraemia; decreased libido; micturition disorders; mydriasis; paraesthesia; QT prolongation.
- *Uncommon*: anxiety; convulsion; diarrhoea; facial oedema; galactorrhoea; hepatic impairment (e.g. cholestatic liver disease); hypertension; hypomania; insomnia; mania; nightmare; raised intraocular pressure; rash; tinnitus; tongue oedema; urinary retention; urticaria; vomiting.

- *Rare*: abnormal LFTs; alopecia; arrhythmia; blood dyscrasias (e.g. agranulocytosis, leucopenia); reduced appetite; delirium; gynaecomastia; hallucinations; jaundice; paralytic ileus.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Amitriptyline is a substrate of CYP1A2, CYP2C9, CYP2C19 (major), CYP2D6 (major), CYP3A4, UGT1A3, and UGT1A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- If a strong CYP2D6 inhibitor (e.g. fluoxetine, paroxetine, quinidine) or strong CYP2C19 inhibitor (e.g. fluconazole, omeprazole) is added to amitriptyline treatment, a lower dose of amitriptyline should be considered. There is a risk of prolongation of the QT interval (see ➔ *Contraindications and cautions*, p. 109).
- *Haloperidol*—may increase the plasma concentration of amitriptyline.
- *Methylphenidate*—may inhibit the metabolism of amitriptyline as a degree of competitive inhibition may develop.
- Smoking may lead to faster metabolism of amitriptyline. Dose adjustments may be necessary upon smoking cessation (see Box 1.11).

Pharmacodynamic

- Amitriptyline is associated with a conditional risk of prolongation of the QT interval. There is a potential risk that co-administration with other drugs that prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 109).
- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (➔ *Contraindications and cautions*)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *SSRIs*, *tapentadol*, *tramadol*, *trazodone*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticholinergics*—increased risk of adverse effects.
- *Antidiabetics*—impaired glycaemic control.
- *Anti-epileptics*—amitriptyline antagonizes the effect.
- *Antihypertensives*—possible increased risk of hypotension.
- *CNS depressants*—additive sedative effect.
- *Domperidone*—may inhibit prokinetic effect.
- *Metoclopramide*—may inhibit prokinetic effect.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).

- *Nefopam*—increased risk of anticholinergic adverse effects and seizures (and serotonin toxicity).
- *SNRIs/SSRIs*—increased risk of seizures (and serotonin toxicity).
- *Sympathomimetics* (e.g. *adrenaline*, *phenylpropanolamine*, *salbutamol*)—combination may predispose patients to cardiac arrhythmias and hypertension.
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

All indications

- 10mg to 25mg PO ON, increasing as necessary to a maximum of 150mg PO daily in divided doses.
- *Amitriptyline should be given at a 50% dose reduction to patients who are known, or suspected, to be CYP2C19 and CYP2D6 poor metabolizers due to the increased risk of dose-dependent adverse effects.*

Dose adjustments

Elderly

- No specific dose reductions are recommended in the SmPC. However, it is suggested that elderly patients are initiated on the lower end of the usual range, i.e. 10mg PO ON, and the dose increased as necessary and as tolerated. Elderly patients are particularly susceptible to adverse anticholinergic effects, with an increased risk for cognitive decline and dementia. Nortriptyline is the preferred choice in the elderly if a TCA is indicated.

Hepatic/renal impairment

- There are no specific instructions for dose reduction in hepatic impairment. It is contraindicated for use in *severe* hepatic impairment and should be used with caution in patients with mild to moderate hepatic impairment. If the drug must be used, the patient should be closely monitored and the lowest effective dose should be prescribed.
- The SmPC states that amitriptyline can be given in usual doses to patients with renal failure. The lowest effective dose should be prescribed.

Additional information

- May have immediate benefits in treating insomnia or anxiety; antidepressant and analgesic effects may be delayed by 2–4 weeks.
- Nortriptyline may be preferred when treating the elderly due to reduced sedative and anticholinergic effects.
- If used for longer than 6 weeks, most antidepressants can cause withdrawal symptoms if they are stopped or rapidly reduced.

Pharmacology

Amitriptyline is a tertiary amine TCA. It is an inhibitor of both SERT and NET (some sources suggest it has a greater effect on SERT), which explains its primary mechanism of action via inhibition of neuronal reuptake of

serotonin and noradrenaline. As well as blocking sodium channels, amitriptyline affects numerous receptors with varying degrees of affinity, which will have an impact on both therapeutic and adverse effects. It is more sedating and has increased anticholinergic properties, compared to other TCAs. Amitriptyline has a strong affinity for, and acts as an antagonist (or inverse agonist) at M_{1-5}, H_1, α_1, and 5-$HT_{2A/2C}$ receptors. It has been shown to bind (with a moderate or lesser affinity) to 5-HT_{2B}, 5-HT_3, 5-HT_6, 5-HT_7, D_1, D_2, D_3, and σ_1 receptors; the clinical significance of these actions is uncertain.

Amitriptyline undergoes hepatic metabolism by a variety of cytochromes (CYP1A2, CYP2C9, CYP2C19—major, CYP2D6—major, and CYP3A4) to the primary active metabolite nortriptyline (which has a greater affinity for NET than for SERT). Further metabolism involves glucuronidation, followed by excretion in urine. Only small amounts are excreted via bile or as unchanged drug in urine.

Reference

1. van den Beuken-van Everdingen MH, de Graeff A, Jongen JL, *et al*. Pharmacological treatment of pain in cancer patients: the role of adjuvant analgesics, a systematic review. *Pain Pract*. 2017;**17**(3):409–19.

Anastrozole

Arimidex® (POM)
Tablet: 1mg (28).

Generic (POM)
Tablet: 1mg (28).

Indications

- Treatment of hormone receptor-positive advanced breast cancer in post-menopausal women.
- Adjuvant treatment of hormone receptor-positive early invasive breast cancer in post-menopausal women.

Contraindications and cautions

- Anastrozole is contraindicated for use in:
  - premenopausal women; pregnant or lactating women.
- Use with caution in:
  - patients with severe renal impairment (CrCl <20mL/min)
  - patients with moderate or severe hepatic disease.
- Asthenia (weakness) and drowsiness have been reported with use of anastrozole. Caution should be observed when driving or operating machinery while such symptoms persist. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: arthritis; asthenia; headache; hot flushes; joint pain; nausea; osteoporosis; rash.
- *Common*: alopecia; anorexia; bone pain; carpal tunnel syndrome; diarrhoea; drowsiness; hypercholesterolaemia; increased LFTs (ALP; ALT; myalgia; paraesthesia; abnormal taste; vaginal bleeding (if persisting after a first few weeks of treatment, further evaluation needed); vaginal dryness; vomiting.
- *Uncommon*: increased LFTs (GGT and bilirubin); hepatitis; hypercalcaemia; trigger finger; urticaria.
- *Rare*: cutaneous vasculitis; erythema multiforme.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Anastrozole is a substrate of CYP3A4 and UGT1A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

- The clinical significance of co-administration with CYP3A4 inducers (see ➔ *Inducers* on the inside back cover) is unknown, but in theory, this combination could reduce the effectiveness of anastrozole.

Pharmacodynamic

- *Oestrogens*—may antagonize the effect of anastrozole.
- *Tamoxifen*—may reduce the beneficial effect of anastrozole.

Dose

- 1mg PO OD.

Dose adjustments

Elderly

- No dosage adjustments are necessary.

Hepatic/renal impairment

- No dose change is recommended in patients with mild hepatic disease. The manufacturer states that anastrozole should be used on a benefit–risk basis for patients with moderate or severe hepatic disease.
- No dose change is recommended in patients with mild or moderate renal impairment, but anastrozole should be used with caution in patients with severe renal impairment (GFR <30mL/min).

Pharmacology

Anastrozole is a potent and selective non-steroidal aromatase inhibitor which does not possess any progestogenic, androgenic, or oestrogenic activity. It is believed to work by significantly lowering serum oestradiol concentrations through inhibition of aromatase (converts adrenal androstenedione to oestrone, which is the precursor of oestradiol). Many breast cancers have oestrogen receptors and growth of these tumours can be stimulated by oestrogens.

Antacid and oxetacaine

Unlicensed special (POM)

Oral suspension (sugar-free): each 5mL contains *oxetacaine* 10mg, *aluminium hydroxide* 200mg, and *magnesium hydroxide* 100mg (150mL).

See ➔ *Additional information*, p. 117 for supply issues.

Indications

- Short-term management of:
  - [+]mucositis[(1)]
  - [+]painful oral candidosis.[(1)]

Contraindications and cautions

- Avoid use in acute GI conditions (e.g. acute inflammatory bowel disease, abdominal pain of unknown origin, intestinal obstruction).
- Avoid use in patients with hypophosphataemia (aluminium binds phosphate).
- Use with caution in patients with renal impairment or those undergoing haemodialysis (see ➔ *Dose adjustments*, p. 117).
- Do not exceed a daily dose of 60mL, as the risk of adverse effects will increase accordingly.
- The use of antacid and oxetacaine should be viewed as a short-term treatment for the painful oral condition, while the underlying cause is treated or improves.

☹ Adverse effects

The frequency is not stated, but adverse effects include:

- constipation; diarrhoea; hypersensitivity reactions (e.g. angioedema, glossitis, pruritus).

At doses of >60mL/day, adverse effects include:

- dizziness; drowsiness; faintness; hyperaluminaemia (may occur in renal impairment; symptoms include apparent dementia and encephalopathy); hypermagnesaemia (may occur in renal impairment; symptoms include nausea, vomiting, confusion, and drowsiness).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Antacid and oxetacaine can influence the rate and extent of absorption of a variety of drugs. For example, it should not be given within 1 hour of the following drugs/formulations:
  - *bisacodyl*—may remove the enteric coat and increase the risk of dyspepsia
  - *demeclocycline*—reduced absorption
  - *diazepam*—absorption may be delayed
  - *digoxin*—possible reduced absorption
  - *enteric-coated formulations*
  - *ferrous sulfate*—possible reduced absorption

- *gabapentin*—reduced absorption
- *lansoprazole*—reduced absorption
- *paroxetine*—reduced absorption of suspension
- *rabeprazole*—reduced absorption.

Pharmacodynamic

- *Opioids*—risk of respiratory depression (associated with hypermagnesaemia).

Dose

- 5mL to 10mL PO 15 minutes before meals and at bedtime. A maximum daily dose of 60mL should not be exceeded.
- The dose can be reduced gradually as symptoms improve.

Dose adjustments

Elderly

- No specific guidance is available. Nonetheless, unless the patient has renal impairment, usual adult doses can be used.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. Nonetheless, use with caution in patients with severe hepatic impairment due the possible risk of subsequent renal impairment.
- Hypermagnesaemia and hyperaluminaemia can develop in patients with renal impairment. Use lower doses or choose an alternative.
- Hyperaluminaemia can also develop in patients undergoing haemodialysis.

Additional information

- Antacid and oxetacaine is an unlicensed product which is available as a special order from Rosemont Pharmaceuticals (Tel. 0800 919312). Delivery is approximately 2 days from making the order. Advise patients to request a prescription at least 4 days before the supply is needed.
- Review the expiry date of the product; it has a shelf-life of 9 months.

Pharmacology

As the name suggests, this product reduces gastric pH, while forming a gel that coats and protects damaged mucosa. Partly due to the adherent nature of the aluminium/magnesium vehicle, oxetacaine produces a topical anaesthetic effect that is both more potent and prolonged than with lidocaine. Only small amounts of aluminium or magnesium are absorbed from the bowel, while the absorbed oxetacaine undergoes rapid and extensive metabolism.

Reference

1. Barber C, Powell R, Ellis A, Hewett J. Comparing pain control and ability to eat and drink with standard therapy vs Gelclair: a preliminary, double centre, randomised controlled trial on patients with radiotherapy-induced oral mucositis. *Support Care Cancer*. 2007;**15**(4):427–40.

Apixaban

Eliquis® (POM)

Tablet: 2.5mg (*yellow*—10; 20; 60); 5mg (*pink*—28; 56).

Indications

- Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, and transient ischaemic attack.
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

Contraindications and cautions

- Apixaban is contraindicated for use in the following circumstances:
  - active clinically significant bleeding
  - concomitant treatment with any other anticoagulants, except under specific circumstances or switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter
  - hepatic disease associated with coagulopathy and clinically relevant bleeding risk
  - presence of malignant neoplasms at high risk of bleeding
  - risk of a major bleed (e.g. GI ulceration—current or recent).
- For instructions on the management of bleeding—see the current edition of the *BNF*.
- Concomitant use of apixaban with combined CYP3A4/P-gp inhibitors (e.g. *ketoconazole*, *posaconazole*) is not recommended due to increased bleeding risk.
- Concomitant use of apixaban with CYP3A4/P-gp inducers (e.g. *rifampicin*) is not recommended (treatment of DVT/PE)/should be used with caution (NVAF).
- The manufacturer does not recommend the use of apixaban in patients with severe hepatic impairment.
- Use with caution in:
  - combination with CYP3A4 inhibitors (see *Drug interactions*, p. 119)
  - mild or moderate hepatic impairment (see *Dose adjustments*, p. 120)
  - prosthetic heart valves (efficacy not established)
  - severe renal impairment (see *Dose adjustments*, p. 120).
- Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: anaemia; contusion; epistaxis; raised GGT; haematuria; haemorrhage (eye, GI, gingival, haematoma, rectal, urogenital, abnormal vaginal); hypotension; nausea; rash; thrombocytopenia.
- *Uncommon*: haematochezia; haemoptysis; haemorrhage (brain, haemorrhoidal, mouth, muscle); hypersensitivity; raised LFTs; pruritus.
- *Rare*: haemorrhage (respiratory tract, retroperitoneal).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Apixaban is a substrate of CYP3A4/5 and P-gp. Minor pathways include CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2J2. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *CYP3A4/P-gp inhibitors (strong)*—concomitant treatment is not recommended in the SmPC.
- *CYP3A4 inhibitors*—the SmPC states no dose adjustments are necessary when apixaban is co-administered with drugs that are not strong inhibitors of both CYP3A4 and P-gp.
- *CYP3A4/P-gp inducers (strong)*—apixaban is not recommended for treatment of DVT and PE, as efficacy may be compromised; apixaban should be used with caution for prevention of stroke and systemic embolism.
- The effect of *grapefruit juice* is unknown.

Pharmacodynamic

- The following drugs increase the risk of bleeding:
  - *aspirin*
  - *clopidogrel*
  - *corticosteroids*
  - *NSAIDs*
  - *SSRIs/SNRIs*.

Dose

The manufacturer recommends that LFTs are performed prior to initiating apixaban.

For prevention of stroke and systemic embolism

- 5mg PO BD.
- For patients ≥80 years of age, with body weight ≥60kg or serum creatinine (SeCr) ≥133micromol/L, the recommended dose is 2.5mg PO BD.

For treatment of DVT and PE, and prevention of recurrent DVT and PE

- Initial treatment of acute DVT or PE—10mg PO BD for 7 days, followed by 5mg PO BD.
  - Treatment duration of at least 3 months should be considered if DVT or PE is provoked by major transient risk factors (i.e. recent major surgery or trauma).
- Prevention of recurrent DVT and PE (following completion of at least 6 months' therapy of 5mg PO BD, or other anticoagulant)—2.5mg PO BD.

Dose adjustments

Elderly

- The manufacturer recommends a dose of 2.5mg PO BD in patients ≥80 years of age for management of NVAF.

Hepatic/renal impairment

- Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Dose adjustments are not required in patients with mild or moderate hepatic impairment.
- The manufacturer advises caution when using apixaban in patients with severe renal impairment (CrCl 15–29mL/min). The following recommendations apply:
  - for treatment of DVT and PE and prevention of recurrent DVT and PE, apixaban is to be used with caution
  - for prevention of stroke and systemic embolism in patients with NVAF, the dose should be reduced to 2.5mg PO BD.
- Dose adjustments are not required in patients with mild or moderate renal impairment.
- Use is not recommended in patients with CrCl <15mL/min or those on dialysis, due to lack of clinical data.

Additional information

- Tablets may be crushed and mixed with water, GLU, or apple juice/puree immediately prior to use and administered orally. The crushed tablet can also be given in 60mL of water or G5W and given immediately via a nasogastric tube, which should be flushed after administration.
- Refer to the SmPC for information about changing from, or to, other anticoagulants.

Pharmacology

Apixaban is a highly selective direct factor Xa inhibitor. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathways of the blood coagulation cascade, inhibiting both thrombin formation and the development of thrombi. Apixaban has no direct effects on platelet aggregation. Apixaban has an oral bioavailability of approximately 50%. It is a substrate of P-gp. Approximately 25% of a dose is metabolized to inactive metabolites, with renal excretion accounting for approximately 27% of total clearance.

Aprepitant

Emend® (POM)
Capsule: 80mg (2); 125mg (1; 5).

Generic (POM)
Capsule: 80mg (2); 125mg (1; 5).

Indications

- Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy.
- †Refractory nausea and vomiting.[1]
- †Refractory chronic cough.[2]

Contraindications and cautions

- Contraindicated for use in patients with acute porphyria.
- Use with caution in the following circumstances:
  - CYP2C9/CYP3A4 substrates (see ➔ *Drug interactions*); moderate hepatic impairment (see ➔ *Dose adjustments*, p. 122).

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: appetite reduced; constipation; dyspepsia; fatigue; headache; hiccups; elevated LFTs.
- *Uncommon*: abdominal pain; acne; anaemia; anxiety; asthenia; dizziness; dry mouth; dysuria; flatulence; gastro-oesophageal reflux disease; hot flushes; febrile neutropenia; malaise; palpitations; rash; somnolence.
- *Rare*: abdominal distension; bradycardia; candidosis; conjunctivitis; cough; disorientation; dysgeusia; euphoria; hyperhidrosis; lethargy; muscle spasm; oedema; photosensitivity reaction; pollakiuria; polydipsia; post-nasal drip; sneezing; Stevens–Johnson syndrome; stomatitis; tinnitus; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Aprepitant is a substrate, a moderate inhibitor, and an inducer of CYP3A4. The inhibitory effect on CYP3A4 appears during early treatment, but after 7 days, the modest induction effect on CYP3A4 is prevalent. The effect on CYP3A4 is more pronounced for orally administered drugs than for the parenteral route. Aprepitant is also a moderate inducer of CYP2C9. After 3 days' treatment with aprepitant, CYP2C9 and CYP3A4 activity returns to baseline within 2 weeks. Prolonged use of aprepitant, as may occur with unlicensed indications, would be expected to maintain the induction effect. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

- Refer to the SmPC for details discussing drug interactions involving CYP2C9 and CYP3A4. Co-prescribed drugs that may be of concern include clarithromycin, dexamethasone (oral), midazolam (oral), oxycodone (oral), voriconazole, and warfarin.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).

Dose

For prevention of nausea and vomiting

- Initial dose 125mg PO OD taken 1 hour before chemotherapy, then 80mg PO OD for 2 days.
- Taken in conjunction with dexamethasone and a 5-HT_3 antagonist (refer to the SmPC for further details).

†For refractory nausea and vomiting

- A report in two patients describes aprepitant 80mg PO OD for up to 4 months' continual treatment.[1]

†For refractory chronic cough

- One small study reported 7-day treatment with aprepitant for chronic cough in lung cancer patients.[2]
- Initial dose 125mg PO OD on day 1, followed by 80mg PO OD until day 7.

Dose adjustments

Elderly

- Usual adult doses recommended.

Hepatic/renal impairment

- Dose adjustments are unnecessary for patients with mild hepatic impairment. There are limited data in patients with moderate hepatic impairment, and no data in patients with severe hepatic impairment. The SmPC advises caution in these patients.
- Dose adjustments are unnecessary for patients with renal impairment, including those undergoing haemodialysis.

Additional information

- The capsules must be swallowed whole, with or without food.

Pharmacology

Aprepitant is a selective high-affinity antagonist of substance P/neurokinin 1 (NK_1) receptors. The oral bioavailability of aprepitant is approximately 60–65%. Aprepitant undergoes extensive hepatic metabolism, primarily by CYP3A4, with minor involvement of CYP1A2 and CYP2C19. Seven weakly active metabolites have been identified. Aprepitant is not renally excreted.

References

1. Lowery L, Andrew I, Gill S, Lee M. The use of aprepitant in a case of refractory nausea and vomiting. *Palliat Med*. 2014;**28**(7):990–1.
2. Prabhash K, Noronha V, Bhattacharjee A, *et al*. Aprepitant for cough suppression in advanced lung cancer: a randomized trial. *J Thorac Oncol*. 2018;**13**(10 Suppl):S360.

Baclofen

Lioresal® (POM)

Tablet: 10mg (100).
Liquid (sugar-free): 5mg/5mL (300mL).
Solution for injection: 50 micrograms/mL.
Solution for infusion: 500 micrograms/mL (20mL).

Generic (POM)

Tablet: 10mg (84).
*Liquid**: 5mg/5mL (300mL).
Solution for injection: 50 micrograms/mL.
Solution for infusion: 500 micrograms/mL (20mL); 2mg/mL (5mL; 20mL).

Indications

- Relief of spasticity of voluntary muscle.
- ✢Hiccup.[1]

Contraindications and cautions

- Avoid in patients with active peptic ulceration.
- Baclofen should be used cautiously in the following conditions since it may lead to exacerbations:
  - confusional states
  - depressive or manic disorders
  - epilepsy
  - Parkinson's disease
  - schizophrenia.
- Baclofen should also be used cautiously in the following conditions:
  - cerebrovascular accident
  - diabetes mellitus (baclofen may cause a rise in blood glucose)
  - hepatic impairment (baclofen may elevate LFTs)
  - hypertension (see ➔ *Drug interactions*, p. 124)
  - renal impairment (see ➔ *Dose adjustments*, p. 125)
  - respiratory impairment (see ➔ *Adverse effects*, p. 124).

• Treatment should always be discontinued over a period of about 1–2 weeks by gradual dosage reduction unless a serious adverse event has occurred. Abrupt withdrawal can precipitate symptoms such as anxiety, confusion, convulsions, dyskinesia, hallucinations, mania, paranoia, psychosis, and tachycardia. These symptoms may occur within a few hours after discontinuation. In addition, rebound temporary aggravation of spasticity can also occur. If such symptoms occur, the dose should be reinstated and a longer withdrawal should be planned. In exceptional circumstances, a CSCI may be used short term for the management of withdrawal.

* Check each generic product for sugar content.

- Baclofen may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: nausea; sedation; somnolence.
- *Common*: ataxia; CV depression; confusion; constipation; depression; diarrhoea; dizziness; dry mouth; dysuria; enuresis; euphoria; fatigue; hallucinations; headache; hypotension; insomnia; muscular weakness; myalgia; nightmares; nystagmus; rash; respiratory depression; sweating; tremor; visual disturbances; vomiting.
- *Rare*: abnormal LFTs; abdominal pain; dysarthria; dysgeusia; erectile dysfunction; paraesthesia; urinary retention.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- *ACE-Is*—may reduce renal excretion of baclofen.
- *Diuretics*—may reduce renal excretion of baclofen.
- *NSAIDs*—may reduce renal excretion of baclofen.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Antihypertensives*—additive hypotensive effect.
- *CNS depressants*—increased risk of adverse effects such as sedation and respiratory depression.
- *Lithium*—combination can result in aggravated hyperkinetic symptoms.
- *Sativex*®—theoretical increased potential for reduced muscle tone and power, with subsequent risk of falls.
- *TCAs*—effect of baclofen may be potentiated.

Dose

Muscle spasticity/spasm

- Initial dose of 5mg PO TDS, increasing by 5mg PO TDS every 3 days until satisfactory control is achieved or a dose of 20mg PO TDS is reached. The dose can be increased further under supervision to a maximum daily dose of 100mg.
- Patients may require a slower titrating schedule if adverse effects become problematic.
- †A single case study describes the successful use of baclofen via CSCI.[2] A dose of 10mg over 24 hours was administered for 4 days to prevent withdrawal symptoms in a patient approaching the end of life.

†*Hiccup*

- Initial dose of 5mg PO BD, increasing to 10mg PO BD after 3 days. Further dose increases may be necessary, to a maximum of 20mg PO TDS.

Dose adjustments

Elderly

- No specific dose reductions are necessary, but lower initial doses are recommended (e.g. 2.5mg to 5mg PO BD). Further titration should be cautious. Also refer to ➔ *Hepatic/renal impairment*.

Hepatic/renal impairment

- For liver impairment, no specific guidance is available. Dose requirements should be individually titrated.
- Baclofen is substantially excreted by the kidney and dose reductions will be necessary in those with impaired renal function. The manufacturer recommends that an initial low dose (e.g. 5mg PO OD) should be used and the patient should be observed for signs of toxicity if the dose is increased further. Only use in end-stage renal failure if perceived benefit outweighs the risk.

Additional information

- If the patient develops hypotonia which is considered problematic during the day, increasing the evening dose and reducing the daytime dose(s) may overcome this issue.

➔ Pharmacology

Baclofen is a GABA derivative that is a specific agonist at GABA-B receptors. The precise mechanism of action is not fully understood and there is no conclusive evidence that actions on GABA systems lead to clinical effects. Nonetheless, it inhibits reflexes at the spinal level and actions at supraspinal sites may also occur. The clinical effect in hiccups may be due to a direct effect on the diaphragm. Baclofen is rapidly and extensively absorbed, and is excreted primarily by the kidney in unchanged form (approximately 85% of the dose is excreted unchanged).

References

1. Adam E. A systematic review of the effectiveness of oral baclofen in the management of hiccups in adult palliative care patients. *J Pain Palliat Care Pharmacother*. 2020;**34**(1):43–54.
2. Rémi C, Albrecht E. Subcutaneous use of baclofen. *J Pain Symptom Manage*. 2014;**48**(2):e1–3.

Benzydamine

Difflam® (P)
Oral rinse: benzydamine hydrochloride 0.15% w/v (300mL).
Oromucosal spray: benzydamine hydrochloride 0.15% w/v (30mL).

Generic (P)

Mouthwash: benzydamine hydrochloride 0.15% w/v.
Oromucosal spray: benzydamine hydrochloride 0.15% w/v.

Indications

- Painful inflammatory conditions of the mouth and throat.

Contraindications and cautions

- Oral rinse should generally be used undiluted. Should stinging occur, it can be diluted with an equal volume of water.
- The use of benzydamine should be viewed as a short treatment (7 days) for the painful oral condition, while the underlying cause is treated or improves. Use beyond this should be under medical supervision.
- The oral rinse contains alcohol 10%.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Uncommon*: numbness (local); stinging (local).
- *Very rare*: bronchospasm; hypersensitivity (very rarely reported, but include bronchospasm, pruritus, rash, and urticaria); laryngospasm.

Drug interactions

Pharmacokinetic

- None known.

Pharmacodynamic

- None known.

Dose

Oral rinse

- 15mL, as an oral rinse or gargle, every 1.5 to 3 hours as required. The patient must not swallow.

Oromucosal spray

- 4 to 8 sprays to the affected area every 1.5 to 3 hours as required.

Dose adjustments

Elderly

- No adjustments necessary.

Hepatic/renal impairment

- Systemic absorption with correct use is minimal, so dose adjustments are unnecessary for patients with renal or hepatic impairment.

Pharmacology

Benzydamine is an NSAID, thought to produce anti-inflammatory and analgesic actions by stabilizing the cellular membrane and inhibiting prostaglandin synthesis.

Bethanechol

Myotonine® (POM)
Tablet: 10mg (100); 25mg (100).
An oral suspension can be made extemporaneously (see ➔ *Additional information*, p. 128).

Indications

- ✢Xerostomia.[1]–[3]
- Urinary retention (not discussed).

Contraindications and cautions

- The manufacturer only describes the following contraindications:
  - intestinal anastomosis (recent)
  - intestinal obstruction
  - myocardial infarction (recent)
  - urinary obstruction.
- At the doses employed for xerostomia, bethanechol is well tolerated. Nonetheless, bethanechol should be used with caution in the following conditions:
  - asthma (may cause bronchoconstriction)
  - bradycardia
  - coronary artery disease
  - epilepsy
  - hyperthyroidism (may precipitate atrial fibrillation)
  - hypotension
  - narrow-angle glaucoma
  - parkinsonism
  - peptic ulcer (increases gastric acid secretion)
  - vasomotor instability.
- Due to potential for postural hypotension, patients may be warned to avoid driving until the effects of bethanechol are known. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency of adverse effects is not stated, but the following have been reported:

- abdominal pain; bronchoconstriction; diarrhoea; dizziness; headache; lacrimation; malaise; miosis; nausea; postural hypotension; rhinorrhoea; sweating; urinary urgency; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- The pharmacokinetics of bethanechol are unknown.
- No recognized pharmacokinetic interactions.

Pharmacodynamic

- *Anticholinergics*—antagonism of effect.

- *Domperidone*—prokinetic effect may be enhanced.
- *Laxatives*—increased risk of diarrhoea.
- *Metoclopramide*—prokinetic effect may be enhanced.
- *Tramadol*—may increase the risk of seizures.

Dose

+Xerostomia

- 25mg PO BD to TDS, preferably taken 1 hour before or 2 hours after meals to avoid nausea or vomiting.
- A lower dose (e.g. 10mg PO BD to TDS) can be tried if excessive salivation occurs.

Dose adjustments

Elderly

- No dose adjustments necessary.

Hepatic/renal impairment

- The pharmacokinetics of bethanechol are unknown. The manufacturer makes no recommendation for dose adjustments.

Additional information

- Bethanechol is stated to have fewer adverse effects than pilocarpine in the management of xerostomia.
- An oral suspension (5mg/mL) can be made extemporaneously using 10mg tablets × 50 in a suitable vehicle (e.g. cherry/simple syrup; Ora-Sweet® SF) to 100mL. The suspension has an expiry date of 60 days at room temperature (25°C).[4]

Pharmacology

Bethanechol chloride is a quaternary ammonium choline ester muscarinic agonist. Due to its polarity, bethanechol does not readily cross the blood–brain barrier and is unlikely to produce symptoms such as those displayed by pilocarpine. It is highly specific for the muscarinic receptor, with negligible activity at nicotinic receptors. Due to very slow hydrolysation by acetylcholinesterase, bethanechol is stated to have a prolonged duration of action. Following oral administration, onset of action is within 1 hour. Bethanechol primarily affects the urinary and GI tracts.

References

1. Cotomacio C, Campos L, Simões A, *et al*. Influence of bethanechol on salivary parameters in irradiated patients. *Med Oral Patol Oral Cir Bucal*. 2017;**22**(1):e76–83.
2. Kavitha M, Mubeen K, Vijayalakshmi KR. A study on evaluation of efficacy of bethanechol in the management of chemoradiation-induced xerostomia in oral cancer patients. *J Oral Maxillofac Pathol*. 2017;**21**(3):459–60.
3. Jaguar GC, Lima EN, Kowalski LP, *et al*. Double blind randomized prospective trial of bethanechol in the prevention of radiation-induced salivary gland dysfunction in head and neck cancer patients. *Radiother Oncol*. 2015;**115**(2):253–6.
4. Allen LV, Erickson MA. Stability of bethanechol chloride, pyrazinamide, quinidine sulfate, rifampicin, and tetracycline hydrochloride in extemporaneously compounded oral liquids. *Am J Health Syst Pharm* 1998;**55**(17): 1804–9.

Bicalutamide ♀

Casodex® (POM)
Tablet: 50mg (28); 150mg (28).

Generic (POM)
Tablet: 50mg (28); 150mg (28).

Indications

- Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration (50mg).
- Locally advanced prostate cancer at high risk of disease progression, either alone or as adjuvant treatment to prostatectomy or radiotherapy (150mg).
- Locally advanced, non-metastatic prostate cancer when surgical castration or other medical intervention are inappropriate (150mg).

Contraindications and cautions

- Contraindicated for use in women and children.
- There is a *conditional* risk of QT prolongation/TdP. The SmPC states there is a *potential* risk of QT prolongation/TdP due to androgen deprivation. Due consideration should be given to the risk when considering prescribing for patients with additional risk factors (e.g. electrolyte disorders, concurrent use of drugs known to affect the QT interval).
- Use with caution in the following:
  - coumarin anticoagulant treatment (see ➔ *Drug interactions*, p. 130)
  - liver disease (see ➔ *Dose adjustments*, p. 130).
- Bicalutamide inhibits CYP3A4; the manufacturer advises caution when co-administered with drugs metabolized predominantly by CYP3A4.
- Avoid direct exposure to sunlight as photosensitivity reactions may occur (150mg).
- Bicalutamide may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: abdominal pain; anaemia; asthenia; breast tenderness; constipation; dizziness; gynaecomastia; haematuria; hot flushes; nausea; oedema.
- *Common*: alopecia; altered LFTs (manufacturer recommends checking LFTs periodically); reduced appetite; cardiac failure; chest pain; depression; dry skin; dyspepsia; erectile dysfunction; fatigue; flatulence; hepatotoxicity; hirsutism; jaundice; reduced libido; myocardial infarction (apparent increased risk when used in combination with LHRH agonists); pruritus; rash; somnolence; weight gain.
- *Uncommon*: hypersensitivity reactions (angioedema; urticaria); interstitial lung disease.
- *Rare*: photosensitivity.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Bicalutamide is metabolized by CYP3A4. Although evidence in humans is weak, there is a suggestion it *may* be a strong inhibitor of CYP3A4 (see ➔ *Contraindications and cautions*, p. 129). Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Warfarin*—may be displaced from protein binding sites; check INR if bicalutamide is started in patients already on warfarin.

Pharmacodynamic

- Androgen deprivation therapy may prolong the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.

Dose

Treatment of advanced prostate cancer in combination with LHRH analogue therapy or surgical castration

- 50mg PO OD
- Treatment should be started at least 3 days before commencing treatment with an LHRH analogue or at the same time as surgical castration.

Locally advanced prostate cancer

- 150mg PO OD
- It should be taken for at least 2 years or until the disease progresses.

Dose adjustments

Elderly

- Usual adult doses are recommended.

Hepatic/renal impairment

- Bicalutamide is extensively metabolized in the liver. However, dosage adjustments are not required for patients with mild hepatic impairment. Increased accumulation may occur in patients with moderate to severe hepatic impairment, although no specific guidance is available. Patients should be closely monitored for signs of deteriorating liver function.
- Dosage adjustments are not required for patients with renal impairment.

Additional information

- Although tablets may be crushed and dispersed in water prior to administration, this is not recommended due to the risk of exposure.

Pharmacology

Bicalutamide is a non-steroidal anti-androgen that blocks the action of androgens of adrenal and testicular origin which stimulate the growth of normal and malignant prostatic tissue. It is well absorbed following oral administration, highly protein-bound, and extensively metabolized. The metabolites are eliminated via the kidneys and bile.

Bisacodyl

Generic (P)
Tablet e/c: 5mg (60; 100; 500; 1000).
Suppository: 10mg (12).

Indications

- Treatment of constipation.

Contraindications and cautions

- Contraindicated in:
  - abdominal pain of unknown origin
  - acute inflammatory bowel disease
  - anal fissure (suppository)
  - ileus
  - intestinal obstruction
  - severe dehydration
  - ulcerative proctitis (suppository).

Adverse effects

Refer to the SPC for a full list of adverse effects.

- *Common*: abdominal cramps and pain; diarrhoea; nausea.
- *Uncommon*: abdominal discomfort; anorectal discomfort; dizziness; haematochezia (blood in stool); vomiting.
- *Rare*: anaphylactic reactions; angioedema; colitis; dehydration; hypersensitivity; syncope.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- *Antacids*—may remove the enteric coat and increase the risk of dyspepsia.

Pharmacodynamic

- *5-HT$_3$ antagonists*—antagonize the laxative effect.
- *Anticholinergics*—antagonize the laxative effect.
- *Corticosteroids*—may increase the risk of electrolyte imbalances.
- *Cyclizine*—antagonize the laxative effect.
- *Diuretics*—may increase the risk of electrolyte imbalances.
- *Opioids*—antagonize the laxative effect.

Dose

- Initial dose 5mg to 10mg PO ON. Dose can be increased as necessary to a maximum of 20mg PO ON.
  - †Higher doses may be necessary for opioid-induced constipation (OIC), although other treatment options should be considered.
- Alternatively, 10mg PR OM.
  - †Additional doses may be needed for OIC, although other treatment options should be considered.

Dose adjustments

Elderly

- No specific dose adjustments recommended by the manufacturer.

Hepatic/renal impairment

- No specific dose adjustments recommended by the manufacturer.

Additional information

- Suppositories are usually effective in about 20 minutes; tablets take effect in 6–12 hours.
- Tablets must not be crushed due to risk of dyspepsia.

Pharmacology

Bisacodyl is a locally acting laxative which undergoes bacterial cleavage in the colon to produce stimulation of both the large intestine and the rectum, causing peristalsis and a feeling of rectal fullness.

Buprenorphine ♀

Temgesic® (CD3 POM)

Sublingual tablet: 200 micrograms (50); 400 micrograms (50).
Injection: 300 micrograms/mL (5 × 1mL).

BuTrans® (CD3 POM)

Transdermal patch (7 days): 5 micrograms/hr (4); 10 micrograms/hr (4); 15 micrograms/hr (4); 20 micrograms/hr (4).

Transtec® (CD3 POM)

Transdermal patch (4 days): 35 micrograms/hr (4); 52.5 micrograms/hr (4); 70 micrograms/hr (4).

Generic (CD3 POM)

Sublingual tablet: 200 micrograms (50); 400 micrograms (7; 50).
Transdermal patch (7 days): 5 micrograms/hr (4); 10 micrograms/hr (4); 15 micrograms/hr (4); 20 micrograms/hr (4).
*Transdermal patch (4 days)**: 35 micrograms/hr (4); 52.5 micrograms/hr (4); 70 micrograms/hr (4).
Other buprenorphine products are available but are not suitable for use in the palliative care population.

Indications

- Acute pain (tablets and injection—*not discussed*).
- Treatment of non-malignant pain of moderate intensity unresponsive to non-opioid analgesics (*BuTrans®* patches).
- Management of moderate to severe cancer pain and severe pain unresponsive to non-opioid analgesics (*Transtec®* patches).

Contraindications and cautions

Large numbers of patient safety incidents involving transdermal buprenorphine patches have been reported to the NRLS. The Care Quality Commission/NHS England recommendations[1] are summarized below:

1. Transdermal buprenorphine patches should be restricted to patients who are already receiving regular doses of opioids.
   i. Do not use for acute pain.
   ii. Do not use in opioid-naïve patients (5 micrograms/hr patch is the exception).
2. Before using a transdermal buprenorphine patch, calculate the total daily dose of all the opioid analgesics that the patient has received previously. This is usually in morphine equivalence. Use locally or nationally approved dose conversion charts to do this (also see ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56).

* *Hapoctasin®* brand releases for 3 days only. There may be variation with other products.

3. Determine a new dose of analgesia to be delivered by transdermal buprenorphine patch in morphine equivalents. Ensure the total daily dose is not increased in steps > 50% of the previous daily dose. Note that >1 transdermal buprenorphine patch may have to be used.
4. Patches may be difficult to locate, given their size and colour. Formally record the anatomical position of currently applied patches, so that this information is readily available to inform future decisions and actions.
5. Prescribe transdermal buprenorphine patches by brand to avoid confusing patients or carers.
6. Patients may exhibit symptoms of opioid withdrawal when a transdermal buprenorphine patch has been omitted. Ensure that opioid treatment is reinstated, at lower doses if appropriate.
7. A significant amount of the initial amount of buprenorphine remains in the transdermal patch after the prescribed duration of application (i.e. 3, 4, or 7 days)—ensure adequate disposal is discussed with the patient; patches must be removed and replaced in accordance with the manufacturers' instructions (refer to the SmPC) or, where applicable, local guidelines.

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care. There may, however, be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation). Nonetheless, the SmPC contraindicates buprenorphine for use in patients with:
  - cor pulmonale
  - concurrent administration of MAOIs or within 2 weeks of discontinuation of their use
  - delirium tremens
  - myasthenia gravis (high risk of respiratory depression)
  - severe COPD.
- The SmPCs of transdermal buprenorphine products contraindicate concurrent administration with MAOIs or within 2 weeks of their discontinuation (risk of serotonin toxicity—see ➔ Chapter 1, *Serotonin toxicity*, p. 29). If concomitant use is unavoidable (e.g. *linezolid*), ensure there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 137). Of the opioids, *morphine* is believed to carry the lowest risk. Buprenorphine is also believed to carry a low risk; nonetheless, treatment must be reviewed urgently if symptoms develop, buprenorphine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug

Safety Alert about concurrent use of opioids and benzodiazepines.[2] The SmPC warns that concurrent use of buprenorphine and benzodiazepines (or *zopiclone/zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.

- Transdermal formulations should not be used if the patient has variable analgesic requirements or for the treatment of acute or intermittent pain.
- Naloxone can reverse the effects of buprenorphine (usually needing a continuous infusion of high doses).
- Dose adjustments may be necessary in hepatic impairment (see ➔ *Dose adjustments*, p. 140).
- Use with caution in patients with:
  - concurrent CYP3A4 inhibitors (see ➔ *Drug interactions*)
  - cholecystectomy (risk of spasm of the sphincter of Oddi)
  - convulsive disorders
  - head injury (risk of increased intracranial pressure)
  - hepatic impairment (empirical dose adjustment may be necessary—see ➔ *Dose adjustments*, p. 140)
  - pyrexia (transdermal route only—increased buprenorphine delivery rate)
  - severe respiratory disease (respiratory effects of opioids are more pronounced during sleep).
- Despite the *CredibleMeds® possible* risk of dose-related QT prolongation/TdP with buprenorphine, there are no such warnings in SmPCs in the UK of any of the transdermal formulations (in the United States, warnings exist above 20 micrograms/hr). Nonetheless, due consideration should be given to the risk when considering prescribing for patients with additional risk factors (e.g. electrolyte disorders, concurrent use of drugs known to affect the QT interval).
- Patients should be advised to avoid exposing the patch application site to direct heat sources, such as hot-water bottles, electric blankets, heat lamps, saunas, or baths, because of the risk of increased absorption.
- Patients who experience serious adverse events should have the patches removed immediately and should be monitored for up to 24 hours after patch removal (depot persists for up to 24 hours).
- Treatment with transdermal buprenorphine should not be discontinued abruptly (except in situations described earlier). If treatment with transdermal buprenorphine is to be discontinued, the patient must be switched to a suitable dose of an alternative opioid (e.g. morphine, oxycodone) to enable dose adjustment and avoidance of opioid withdrawal symptoms (see ➔ *Additional information*, p. 140).
- Buprenorphine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown, but buprenorphine is believed to have less of an effect, compared to other opioids.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month). Buprenorphine is believed to have less of an effect, compared to other opioids.
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51). Buprenorphine is believed to have a reduced risk, compared to other opioids (see Chapter 2, *Opioid-induced hyperalgesia and tolerance*).

Adverse effects

Refer to the SmPC for a full list of adverse effects. Frequency of adverse effects varies, depending on formulation. Strong opioids tend to cause similar adverse effects, albeit to varying degrees.

- *Very common*: application site reaction (*delayed allergic reactions may necessitate discontinuation*); constipation; dizziness; drowsiness; erythema; headache; nausea; pruritus; vomiting.
- *Common*: abdominal pain; anorexia; anxiety; asthenia; confusion; depression; diarrhoea; dry mouth; dyspepsia; dyspnoea; exanthema; insomnia; muscle weakness; nervousness; peripheral oedema; QT prolongation (*only appears in the SmPC for high-strength tablets*); rash; sweating; tiredness; tremor.
- *Uncommon*: aggression; agitation; blurred vision; cough; dry eye; dysarthria; dysgeusia; euphoria; flatulence; flushing; hallucinations; hiccups; hypersensitivity; hypertension; hypotension; reduced libido; memory impairment; migraine; nightmares; paraesthesia; restlessness; sleep disorder; syncope; tachycardia; tinnitus; urinary dysfunction; vertigo.
- *Rare*: anaphylaxis; dehydration; dysphagia; erectile dysfunction; ileus; miosis; psychosis; respiratory depression; rhinitis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Buprenorphine is extensively metabolized in the liver by N-dealkylation, via both CYP3A4/5 (major) and CYP2C8, to norbuprenorphine. To a lesser extent, buprenorphine undergoes glucuronidation via UGT1A1, UGT1A3, UGT2B7, and UGT2B17. Norbuprenorphine also undergoes glucuronidation via UGT1A1 and UGT1A3.

- Inhibition of CYP3A4 alone may have a less than expected effect on buprenorphine clearance, due to the impact of glucuronidation. Metabolism of buprenorphine during therapy with transdermal buprenorphine seems unlikely to be affected by co-administration of CYP3A4 inhibitors (i.e. avoids first-pass metabolism).[3] The effect of CYP3A4 inducers (e.g. carbamazepine, enzalutamide, phenobarbital) has not been investigated but would be expected to reduce the efficacy of buprenorphine.
- Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these metabolic enzymes may lead to clinically relevant drug interactions.

Pharmacodynamic

- Buprenorphine may cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *methadone*, *quinine*) may result in ventricular arrhythmias. Refer to the SmPC for further details.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 134.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing affect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine; the prescriber should be aware of the need to reduce the opioid dose.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOI*—risk of severe and unpredictable interactions with MAOIs, involving the potentiation of opioid or serotonergic effects.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 134.

Dose

Transdermal: 7-day patches

Given the wide number of available preparations, brand prescribing is recommended to avoid confusion.

- For moderate pain unresponsive to non-opioids, i.e. suitable for opioid-naïve patients:
  - initial dose of 5 micrograms/hr patch for 7 days.
- The analgesic effect should not be evaluated for at least 72 hours after application to allow for gradual increase in plasma buprenorphine concentration. Supplementary analgesia should be used as necessary.

- The dose can be adjusted, if necessary, at 3-day intervals using a patch of the next strength or two patches of the same strength (applied at the same time to avoid confusion).
- A maximum of two patches can be used at any one time.
- The same site should be avoided for at least 3–4 weeks.
- Refer to ➔ Chapter 2, *Breakthrough cancer pain*, p. 54 for guidance relating to BTcP.

Transdermal: 3- to 4-day patches

Given the wide number of available preparations, brand prescribing is recommended to avoid confusion.

- *Despite the SmPC indication, these patches must not be initiated in opioid-naïve patients.*
- For moderate to severe cancer pain and severe pain unresponsive to non-opioids:
  - initial dose of buprenorphine is based upon previous opioid requirements
  - the SmPC states that for opioid-naïve patients, 35 micrograms/hr for 96 hours should be used.
  - *NB—this is equivalent to approximately 80mg/day PO morphine.*
- The analgesic effect should not be evaluated for at least 24 hours after application to allow for gradual increase in plasma buprenorphine concentration. Supplementary analgesia should be used as necessary (the SmPC suggests rescue doses of buprenorphine 200 micrograms to 400 micrograms SUBLING every 24 hours).
  - Alternatively, it is common practice to use rescue doses of an oral opioid, such as morphine, every 1–2 hours PRN (calculated as one-tenth to one-sixth of the patch strength dose); for example, for a 35 micrograms/hr buprenorphine patch, a suitable rescue dose would be morphine 10mg to 15mg PO every 1–2 hours PRN.
- The dose can be adjusted, if necessary, at intervals of no longer than 96 hours, using a patch of the next strength or using two patches of the same strength (applied at the same time to avoid confusion).
- A maximum of two patches can be used at any one time.
- The same site should be avoided for at least 7 days (see ➔ *Additional information*, p. 140).
- Refer to ➔ Chapter 2, *Breakthrough cancer pain*, p. 54 for guidance relating to BTcP.

Sublingual

- There are better options for the management of chronic pain.
- For opioid-naïve patients: 200 micrograms to 400 micrograms SUBLING every 6–8 hours PRN.
- Onset of action generally occurs within 30 minutes.
- Duration of action is usually 6–8 hours.

+Subcutaneous

- For opioid-naïve patients: 300 micrograms via CSCI over 24 hours (approximately equivalent to 10mg morphine CSCI).

- Rescue doses (calculated as *one-sixth* to *one-tenth* of the background dose) can be administered via SUBCUT injection every 2–4 hours as needed, although practicality will reduce the maximum dose to 600 micrograms (= 2mL) per injection site.
- In theory, a CSCI could be used to supplement analgesia in a patient receiving a transdermal formulation of buprenorphine.

Dose adjustments

Elderly

- No dosage adjustments are necessary, although dose requirements should be individually titrated. Note, however, that exposure to buprenorphine may be about 20% lower in elderly volunteers with low body fat than in those with normal or high body fat.

Hepatic/renal impairment

- Buprenorphine undergoes extensive metabolism, yet it is well tolerated in hepatic impairment. It is metabolized mainly through glucuronidation, which is generally considered to be less affected by liver disease. The SmPC states that no dosage adjustment is necessary in mild to moderate hepatic impairment. Buprenorphine may accumulate in patients with severe hepatic impairment and alternative treatment should be sought. If buprenorphine is to continue in such patients, it must be used with caution.
- No dosage adjustments are necessary for patients with renal impairment, although dose requirements should be individually titrated.

Additional information

- The following is a guide on how to initiate a patch in relation to previous opioid therapy:
  - standard-release hydromorphone/morphine/oxycodone—give regular 4-hourly doses for the **first 12 hours** after applying the patch
  - *12 hourly* modified-release hydromorphone/morphine/oxycodone—give the final oral dose at the **same time** as applying the first patch
  - *24 hourly* modified-release morphine/oxycodone—apply the patch **12 hours after** the final oral dose
  - CSCI—continue the syringe driver for the **first 12 hours** after applying the patch (consider continuing for **18 hours** in the case of switching from CSCI *alfentanil*)
  - in all cases, ensure PRN medication is readily available.
- When converting from hydromorphone, morphine, or oxycodone to buprenorphine, reduce the dose of any concurrent laxatives by 50% and adjust as necessary. Buprenorphine *may* cause less constipation than other opioids.
- Opioid withdrawal symptoms (e.g. nausea, vomiting, diarrhoea, sweating, shivering) can occur in patients after switching from previously prescribed opioids to transdermal buprenorphine. Rescue doses of the previous opioid can be administered to treat these symptoms if warranted.

- It is appropriate to use alternative opioid agonists as rescue doses for BTcP, or dose titration. At clinical doses, there will be no risk of antagonism.
- Patches should be applied to clean, dry, non-irritated skin, and sites rotated regularly to reduce the chance of skin reactions. Absorption of buprenorphine from the transdermal patch may be affected by the application site. The recommended sites for application of transdermal buprenorphine are the upper outer arm, upper chest, upper back, and side of the chest.
- The matrix patch can be cut diagonally[+] to halve the dose.
- Should the transdermal patch cause application site irritation, avoid using a steroid inhaler or cream; the manufacturer states such actions can affect the rate of absorption. The advice is to change to an alternative opioid.
- Buprenorphine patches should be removed prior to MRI due to the risk of heating. A new patch should be applied to a new site post-scan.
- After removal of **7-day patches**, the SmPC states that buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10 to 24 hours). The US SmPC also adds that this is followed by a decline, with an apparent terminal half-life of approximately 26 hours.
- After removal of **3- and 4-day patches**, buprenorphine concentrations steadily decrease and are eliminated with a half-life of approximately 30 hours (range 22 to 36 hours).
- In all cases, if a decision is made to *switch* transdermal buprenorphine to *an oral opioid formulation*, the subsequent opioid should not be administered (regularly) within 24 hours after patch removal. The SmPC states that there is limited information available on the starting dose of other opioids administered after discontinuation of the patch. Given the complexity and variation of buprenorphine pharmacokinetics, the following is a suggested plan:
  - *Standard-release* PO hydromorphone/morphine/oxycodone:
    - ensure usual PRN doses remain prescribed
    - remove the patch
    - determine the equianalgesic dose
    - after a period of at least 24 hours:
      - commence **regular** 4-hourly *standard-release* PO opioid at 50% of the calculated equianalgesic dose
      - ensure the same dose of the *standard-release* PO opioid is prescribed for PRN use
      - *note that the patient may have been using the same standard-release PO opioid for PRN use at different doses while prescribed transdermal buprenorphine*
    - review both regular and PRN doses of the new opioid **daily** for the next **48 hours** after stopping transdermal buprenorphine, and consider switching to modified-release PO opioid at the earliest opportunity.
  - *12 hourly* modified-release PO hydromorphone/morphine/oxycodone:
    - ensure usual PRN doses remain prescribed
    - remove the patch

- determine the equianalgesic dose
- after a period of **24 hours**:
  - commence the *m/r* (*12-hourly*) PO opioid at **50%** of the calculated equianalgesic dose
  - ensure an appropriate dose of the *standard-release* PO opioid is prescribed for PRN use, based on the dose of the *m/r* (*12-hourly*) PO opioid
  - *note that the patient may have been using the same standard-release PO opioid for PRN use at different doses while prescribed transdermal buprenorphine.*
- review both regular and PRN doses of the new opioid daily for the next **48 hours** after stopping transdermal buprenorphine.

– *24 hourly* modified-release PO morphine/oxycodone—avoid until a stable oral dose has been determined.

- Used patches still contain active drug. Patches should be appropriately disposed of, e.g. by folding in half, with the adhesive side inwards.
- Given the pharmacology of buprenorphine, it may have a role in the management of cholestatic pruritus.[4]
- Buprenorphine (parenteral) is reportedly *chemically and physically* compatible under stated conditions with glycopyrronium and haloperidol.[5]

Pharmacology

Buprenorphine is a semi-synthetic opioid described as being a partial MOR agonist, although at clinical doses, it acts like a full agonist (partial agonism in terms of receptor activity level does not necessarily translate to partial analgesic efficacy); no analgesic ceiling affect has been described, even at doses of up to 32mg daily. It is also an ORL-1 agonist, a DOR antagonist, and a KOR inverse agonist. Buprenorphine binds to the MOR with high affinity and prolonged occupancy. Despite this, naloxone can reverse the effects of buprenorphine (usually needing a continuous infusion of high doses) and analgesia can be supplemented with other MOR agonists such as morphine. Buprenorphine has been shown *in vitro* to have a reduced effect at a variant of the MOR (N40D—a polymorphism present in 10–50% of the population); the clinical significance of this is currently unknown. At clinical doses, buprenorphine does not recruit β-arrestin, which is believed to result in reduced analgesic tolerance and respiratory depression (although see norbuprenorphine below). Nonetheless, recent work suggests this may, in fact, be due to low intrinsic efficacy (see Chapter 1, *Glossary of common terms*, p. 10). The DOR, KOR, and ORL-1 effects are believed to attenuate the development of tolerance and hyperalgesia. A full analgesic effect of buprenorphine is believed to involve interaction with two MOR splice variants (both the 7- and 6-TM proteins).

Buprenorphine is highly lipophilic and undergoes extensive metabolism by N-dealkylation, via both CYP3A4/5 and (to a lesser extent) CYP2C8, to form the weakly active metabolite norbuprenorphine. The bioavailability of oral buprenorphine is extremely poor due to first-pass metabolism. Other routes of administration avoid this first-pass effect. Buprenorphine is also metabolized by glucuronidation via UGT2B7 and UGT1A1, with some contribution from UGT1A3 and UGT2B17, to form buprenorphine

3-glucuronide. Norbuprenorphine is also metabolized by glucuronidation via UGT1A1 and UGT1A3 to norbuprenorphine 3-glucuronide. The clinical effects of the glucuronide metabolites are currently unknown. Despite being a MOR agonist with high affinity for KOR and DOR, norbuprenorphine is about 40–50 times less potent an analgesic than buprenorphine. Unlike buprenorphine, norbuprenorphine is a substrate of P-gp and does recruit β-arrestin. This latter property may, in part, contribute to the adverse effects of constipation and respiratory depression displayed by buprenorphine.

Buprenorphine is mainly eliminated through biliary excretion, with up to 30% being excreted in urine. Enterohepatic circulation of buprenorphine occurs through cleavage of glucuronide by intestinal bacteria, which could partly explain the prolonged half-life and pharmacological effects. Since buprenorphine and norbuprenorphine undergo significant glucuronidation (a process generally considered to be less impacted by liver impairment), liver disease or inhibitors of CYP3A4 may have a less than expected effect on buprenorphine clearance. Nonetheless, in patients with severe liver impairment or those receiving CYP3A4 inhibitors, close monitoring is recommended. Renal impairment does not affect the elimination of buprenorphine.

References

1. Care Quality Commission and NHS England. Safer use of controlled drugs—preventing harms from fentanyl and buprenorphine transdermal patches. 2013. Available from: https://webarchive.nationalarchives.gov.uk/20161107130748/https://www.cqc.org.uk/sites/default/files/documents/safer_controlled_drugs_guidance_for_the_web_fentanyl_and_buprenorphine_transdermal_patches_updated_v3.0.pdf. Accessed 6 August 2020.
2. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
3. Feng XQ, Zhu LL, Zhou Q. Opioid analgesics-related pharmacokinetic drug interactions: from the perspectives of evidence based on randomized controlled trials and clinical risk management. *J Pain Res*. 2017;**10**:1225–39.
4. Reddy L, Krajnik M, Zylicz Z. Transdermal buprenorphine may be effective in the treatment of pruritus in primary biliary cirrhosis. *J Pain Symptom Manage*. 2007;**34**(5):455–6.
5. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Calcitonin (salcatonin or salmon calcitonin) ⚠

Generic (POM)

Injection: 50 units/mL (single dose; 5); 100 units/mL (single dose; 5); 400 units/2mL (multi-dose vial; 1).

Must be stored at fridge temperature (between 2°C and 8°C)—see *Additional information*, p. 145.

Indications

- Treatment of hypercalcaemia of malignancy (see *Pharmacology*, p. 145).
- Paget's disease (*not discussed*).
- Prevention of acute bone loss due to sudden immobilization (*not discussed*).

Contraindications and cautions

- Calcitonin is a peptide and as such, it carries a risk of systemic allergic reaction; there have been isolated reports of anaphylactic shock (see *Adverse effects*). Note that *fish allergy* is not a specific contraindication, but it would be advisable to consider a small test dose.
- Generalized or local flushing are common non-allergic effects of calcitonin and should not be confused with an allergic reaction.
- Long-term use of calcitonin is associated with an increased risk of malignancy, although this is unlikely to be of significance in the management of hypercalcaemia of malignancy (<48 hours' treatment).

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: flushing (facial or upper body—usually observed 10–20 minutes after administration); nausea ± vomiting.
- *Common*: dizziness; dysgeusia; fatigue; headache; malignancy (with long-term use); musculoskeletal pain.
- *Uncommon*: hypersensitivity; hypertension; influenza-like illness; injection site reaction; oedema (facial, peripheral, and generalized); polyuria; pruritus; rash (generalized); visual impairment.
- *Very rare*: serious allergic-type reactions (e.g. anaphylaxis; bronchospasm).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None known.

Pharmacodynamic

- *Bisphosphonates*—likely additive calcium-lowering effect.
- *Denosumab*—likely additive calcium-lowering effect.

Dose

Ampoules should be allowed to reach room temperature before SUBCUT or IM use.

Hypercalcaemia of malignancy

- Note that some clinicians recommend a test dose of 50 units SUBCUT in view of the potential for allergic reactions.
- Initial dose—100 units every 6–8 hours SUBCUT/IM.
- The dose may be increased after 24 hours to a maximum of 400 units SUBCUT/IM every 6–8 hours.
- In severe or emergency cases, 10 units/kg by slow IVI in 500mL of NaCl over a period of at least 6 hours.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- No dose adjustments are necessary in patients with hepatic impairment.
- Although calcitonin is extensively metabolized by the kidneys, the clinical significance of impaired renal function is unknown.

Additional information

- The SmPC recommends that calcitonin must be stored at fridge temperature (between 2°C and 8°C).
- Any product that is stored:
  - *below* 2°C should be discarded
  - at room temperature (approximately 25°C) must be used within 3 months (but not exceeding the original expiry date).[1]

Pharmacology

Calcitonin is a potent hypercalcaemic hormone secreted by the parafollicular C cells that causes an array of intracellular effects after binding to the calcitonin receptor (CTR), a G-protein-coupled receptor. CTRs have been described in many tissues throughout the body, including osteoclasts and the kidney. Calcitonin regulates serum calcium (Ca^{2+}) by inhibiting the efflux of Ca^{2+} from bone; in addition, calcitonin promotes renal excretion of Ca^{2+} by decreasing tubular reabsorption. Decreases in serum Ca^{2+} are usually noted within 2 hours of a single dose, but long-term use is limited. Tachyphylaxis is believed to begin to occur within 48 hours of continued administration as a result of downregulation of CTRs. Nonetheless, one case report described the use of calcitonin for 14 days without evidence of tachyphylaxis in a patient with bisphosphonate-resistant hypercalcaemia of malignancy.[2] Calcitonin is mainly metabolized in the kidneys, forming inactive compounds. While clearance is reduced in patients with end-stage renal failure, the clinical significance is unknown.

References

1. Specialist Pharmacy Service. Calcitonin. 2016. Available from: https://www.sps.nhs.uk/medicines/calcitonin/. Accessed 17 January 2019.
2. Dawson C, Todd AM, Walton A. Treatment of bisphosphonate-resistant hypercalcemia of malignancy with calcitonin. *J Palliat Med.* 2014;**17**(10):1084.

Cannabidiol (CBD) ⚠

Generic

Form: cannabidiol is available to buy in a variety of formulations (e.g. drops, capsules) by the general public as a food supplement. Products containing cannabidiol (as an isolated substance) do not fall under the Human Medicines Regulations 2012 definition of a medicinal product. Thus, they are not required to meet good manufacturing practice, including safety, quality, and efficacy standards. Similarly, such products are not controlled under the Misuse of Drugs Act 1971/Misuse of Drugs Regulations 2001.

Indications

- [+]Anorexia.[1]
- [+]Anxiety.[2]
- [+]Cancer pain.[2,3]
- [+]Insomnia.[2]
- [+]Seizures (*not discussed*).

(See ➔ *Additional information*, p. 149 for further advice.)

Contraindications and cautions

- Cannabidiol has been reported to cause dose-related elevations in LFTs (e.g. AST, ALT). These typically occurred in the first 2 months of treatment initiation and were reversible on discontinuation. The majority of ALT elevations occurred in patients taking concomitant valproate (see ➔ *Drug interactions*, p. 148).
- Pre-treatment LFTs are recommended, together with regular checks with long-term treatment (the US manufacturer of licensed product for seizures recommends LFTs at months 1, 3, and 6).
- Patients and carers should be instructed to report any non-specific symptoms shown below that may precede jaundice, as they are an indication for immediate discontinuation of treatment:
  - abdominal pain (right upper quadrant)
  - asthenia
  - anorexia
  - dark urine
  - drowsiness
  - malaise
  - oedema
  - unexplained nausea/vomiting.
- Cannabidiol is used to treat certain forms of treatment-resistant childhood epilepsy. As with all anti-epileptics, there is a risk of precipitating seizures with abrupt withdrawal. It is unclear whether this risk applies to the palliative care indications described above, but prescribers should consider a supervised dose reduction, rather than an abrupt discontinuation.
- Patients should be monitored for signs of suicidal ideation since anti-epileptic drugs have been associated with this behaviour.

- Cannabidiol may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

The frequency is not defined, but reported adverse effects include:

- anaemia; reduced appetite; asthenia; diarrhoea; drowsiness; fatigue; malaise; raised LFTs; rash; weight changes (decrease or increase).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Cannabidiol is metabolized by CYP3A4 and CYP2C19; it is also metabolized, to a lesser extent, by CYP1A1, CYP1A2, CYP2C9, and CYP2D6. *In vitro* data suggest cannabidiol is an inhibitor of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19. There is a potential for both induction and inhibition of CYP1A2 and CYP2B6.[4] The clinical relevance of the effect on these pathways has not been established; nonetheless, co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Clobazam*—cannabidiol produces a 3-fold increase in plasma concentrations of the active metabolite of clobazam.

Pharmacodynamic

- *CNS depressants*—risk of excessive sedation.
- *Sodium valproate*—increases the incidence of elevated LFTs.

Dose

There are no established clinical guidelines for the use of cannabidiol as a medicinal product in the UK. Presently, no studies exist that clearly identify suitable doses, which can range from 15mg to 900mg (in various formulations). In reality, most patients titrate to effect. However, in February 2020, the Food Standards Agency made a recommendation that no more than 70mg a day is taken, unless under medical supervision.[5] This precautionary advice was based on findings by the government's Committee on Toxicity which highlighted the hepatic risks of cannabidiol.

Dose adjustments

Elderly

- No specific guidance is available, although lower starting doses may be preferable.

Hepatic/renal impairment

- No specific guidance is available.

- In mild hepatic impairment, the US SmPC recommends usual doses. In moderate to severe hepatic impairment, dose reductions of between 50% to 80% are suggested.
- No specific guidance is available for renal impairment. However, given the extensive hepatic metabolism and faecal excretion, it is expected that normal doses can be used.

Additional information

- Cannabidiol may offer some therapeutic benefits, but the current paucity of clinical data in humans and risk of drug interactions (see ➔ *Drug interactions*, p. 148 and ➔ *References*) prevent healthcare practitioners from recommending its use. Recent guidance from the NICE (NG144) advises against prescribing cannabidiol to patients for management of chronic pain.[6]
- Patients should be asked about its use during the medicines reconciliation process.

➔ Pharmacology

The exact pharmacology of cannabidiol is unclear because multiple mechanisms of action and several pharmacological effects have been proposed. Unlike delta-9-tetrahydrocannabinol (THC), the effects of cannabidiol are not caused by direct binding to the endocannabinoid receptors CB_1 and CB_2; cannabidiol acts as a non-competitive negative allosteric modulator of CB_1 receptors and may have antagonist actions on the CB_2 receptor. It is also believed to act as a σ_1 receptor antagonist and appears to facilitate neurotransmission mediated by $5\text{-}HT_{1A}$, either as an agonist or by indirect means.

Due to the high lipid solubility of cannabidiol, absorption from the GI tract is erratic and leads to variable pharmacokinetics. Bioavailability from oral administration has been estimated to be as low as 6% due to significant first-pass metabolism. Oral administration results in slower onset of action, lower peak blood levels of CBs, and a longer duration of effects, compared to smoking or vaporization. With chronic use, cannabidiol may accumulate in adipose tissues. In situations that lead to weight loss (e.g. cancer cachexia), subsequent release and redistribution of cannabidiol stored in adipose tissue may result in persistence of CB activity for several weeks post-administration.

Cannabidiol is hepatically metabolized to form 7-hydroxy cannabidiol (7-OH-CBD), primarily by CYP2C19, CYP3A4, and, to a lesser extent, CYP1A1, CYP1A2, CYP2C9, and CYP2D6. This metabolite undergoes further hepatic metabolism, and the resulting metabolites are subsequently excreted primarily in the faeces and, by a much lesser extent, in the urine. The pharmacological activity of these metabolites is unknown.

References

1. Mücke M, Weier M, Carter C, *et al*. Systematic review and meta-analysis of cannabinoids in palliative medicine. *J Cachexia Sarcopenia Muscle*. 2018;**9**(2):220–34.
2. Christensen A, Pruskowski J. The role of cannabidiol in palliative care #370. *J Palliat Med*. 2019;**22**(3):337–8.
3. Piermarini C, Viswanath O. CBD as the new medicine in the pain provider's armamentarium. *Pain Ther*. 2019;**8**(1):157–8.

4. Foster BC, Abramovici H, Harris CS. Cannabis and cannabinoids: kinetics and interactions. *Am J Med.* 2019;**132**(11):1266–70.
5. Food Standards Agency. Food Standards Agency sets deadline for the CBD industry and provides safety advice to consumers. 2020. Available from: https://www.food.gov.uk/news-alerts/news/food-standards-agency-sets-deadline-for-the-cbd-industry-and-provides-safety-advice-to-consumers. Accessed 14 February 2020.
6. National Institute for Health and Care Excellence. Cannabis-based medicinal products. NICE guideline [NG144]. 2019. Available from: https://www.nice.org.uk/guidance/ng144. Accessed 14 February 2020.

Cannabis extract ⚠

Sativex® (CD4-1 POM)
Oromucosal spray: each millilitre contains 27mg THC and 25mg cannabidiol (CBD) (2.7mg and 2.5mg per spray, respectively).

Indications

- Adjunct in moderate to severe spasticity in multiple sclerosis (specialist use only—not recommended by NICE).
- ⁺Intractable cancer pain.[1,2]

Contraindications and cautions

- Contraindicated for use in patients with:
  - known or suspected history or family history of schizophrenia or other psychotic illness
  - significant psychiatric disorder (other than depression).
- Use with caution in patients with:
  - serious CV disease (e.g. arrhythmias, ischaemic heart disease, poorly controlled hypertension, severe heart failure)
  - epilepsy
  - hepatic impairment (see ➔ *Dose adjustments*, p. 152)
  - history of substance abuse (at risk of abusing *Sativex®*)
  - renal impairment (see ➔ *Dose adjustments*, p. 152).
- CBs have CV effects that include tachycardia and transient changes in BP, including episodes of postural hypotension, particularly during initial dose titration when caution is essential.
- *Sativex®* may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: dizziness; fatigue.
- *Common*: amnesia; anorexia; decreased/increased appetite; application site pain; asthenia; attention disorder; balance disorder; constipation; depression; diarrhoea; disorientation; dissociation; drowsiness; dry mouth; dysarthria; dysgeusia; euphoria; glossodynia; lethargy; malaise; memory impairment; mouth ulceration; nausea and/or vomiting; vertigo; visual disturbances.
- *Uncommon*: abdominal pain; application site irritation; delusional perception; hallucinations (auditory/visual); hypertension; oral mucosal discoloration (reported with long-term use); palpitations; paranoia; pharyngitis; stomatitis; suicidal ideation; syncope; tachycardia; tooth discoloration.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- *Sativex®* is metabolized by a variety of cytochromes, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.
- CBs may affect several metabolic enzymes and currently data are lacking. The SmPC states that *in vitro* data suggest that *Sativex®* may inhibit CYP3A4, UGT1A9, and UGT2B7 at clinically relevant concentrations. Similar data suggest that *Sativex®* may also cause the induction of CYP1A2, CYP2B6, and CYP3A4 at clinically relevant concentrations.
- Although no clinically significant drug interactions have been identified during clinical trials or post-marketing, co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, one or more of these pathways may lead to clinically relevant drug interactions.
- Co-administration with *omeprazole* (CYP2C19 inhibitor) did not result in any notable change in parameters.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Baclofen*—theoretical increased potential for reduced muscle tone and power, with subsequent risk of falls.
- *CNS depressants*—risk of excessive sedation.

Dose

All indications

- Complex dose titration is necessary, performed over a period of up to 2 weeks. The dose is to be administered buccally. Refer to the SmPC.
- There should be at least a 15-minute gap between sprays.
- Adverse reactions such as dizziness or other CNS-type reactions may develop at any time. These effects are usually mild and resolve in a few days, but can serve as a useful guide for titration. Consider maintaining the current dose, reducing the dose, or temporarily interrupting treatment, depending on seriousness and intensity.
- These adverse effects may be overcome by increasing the interval between doses or reducing the dose. Patients may need retitrating to achieve a tolerated dosage regimen that gives acceptable pain relief.
- The usual daily dose ranges between four and eight sprays. Doses in excess of 12 sprays daily, although not recommended, may be used if the perceived benefits outweigh the risks.

Dose adjustments

Elderly

- No specific dose recommendations are available. Use the lowest effective dose.

Hepatic/renal impairment

- The SmPC advises that *Sativex®* should be used with care in patients with significant hepatic and/or renal dysfunction. The effect of *Sativex®*

is expected to be exaggerated and prolonged and patients should be frequently reviewed.

Additional information

- *Sativex*® must be stored in a refrigerator (2–8°C). However, once opened and in use, refrigerated storage is not necessary, but it must not be stored above 25°C.
- The product must be disposed of 42 days after opening.
- *Sativex*® is currently subject to a 'do not do' recommendation from NICE.

Pharmacology

There are at least two types of CB receptor: CB_1 and CB_2. CB_1 receptors are found in pain pathways in the brain and spinal cord where they are thought to regulate CB-induced analgesia by attenuating the effects of excitatory neurotransmitters, e.g. glutamate. CB_1 receptors also affect cognition, memory, and motor function. CB_2 receptors have an effect on immune cells and may cause cannabinoids to display anti-inflammatory effects. Cannabis contains many compounds, but the two of significance in cannabis-based medicinal products are tetrahydrocannabinol and cannabidiol. Following buccal administration, maximum plasma concentrations of both tetrahydrocannabinol and cannabidiol typically occur within 2–4 hours. They are both highly lipid-soluble and accumulate in fatty tissue, leading to a prolonged half-life. They may be stored in fatty tissues for up to 4 weeks, leaching out at sub-therapeutic levels. Both CBs undergo a degree of first-pass metabolism, producing active metabolites; further metabolism occurs in the liver via several cytochromes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), although CYP2C9 may have a more predominant role.

References and further reading

1. Lichtman AH, Lux EA, McQuade R, *et al*. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage*. 2018;**55**(2):179–88.e1.
2. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage*. 2010;**39**(2):167–79.
Schneider LS, Frangakis C, Drye LT, *et al*. Heterogeneity of treatment response to citalopram for patients with Alzheimer's disease with aggression or agitation: the CitAD randomized clinical trial. *Am J Psychiatry*. 2016;**173**(5):465–72.

Carbamazepine

Different preparations may vary in bioavailability. Therefore, it is recommended that patients should remain on the same product once treatment has been stabilized. Inclusion of the brand name on the prescription is suggested.

Standard-release

Tegretol® (POM)
Tablet (scored): 100mg (84); 200mg (84); 400mg (56).
Oral suspension (sugar-free): 100mg/5mL (300mL).

Generic (POM)
Tablet: 100mg (28); 200mg (28); 400mg (28).
Oral suspension (sugar-free): 100mg/5mL (300mL).
Suppository: 125mg (5); 250mg (5).

Modified-release

Tegretol Prolonged Release® (POM)
Tablet (scored): 200mg (56); 400mg (56).
Generic (POM)
Tablet (scored): 200mg (56); 400mg (56).

Indications

- Generalized tonic–clonic and partial seizures.
- Trigeminal neuralgia.
- †Neuropathic pain.[1]

Contraindications and cautions

- Carbamazepine is contraindicated for use in patients with:
  - atrioventricular block
  - history of bone marrow depression
  - porphyria.
- Agranulocytosis and aplastic anaemia have been associated with carbamazepine. Ensure patients and/or their carers can recognize signs of blood, liver, or skin disorders, and advise they seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop.
- Avoid abrupt withdrawal, unless clearly indicated, as seizures may be precipitated.
- Use with caution in the following circumstances:
  - angle-closure glaucoma
  - cardiac disease
  - elderly (see *Dose adjustments*, p. 157)
  - hepatic impairment.
- Individuals of Han Chinese and Thai descent should be screened for HLA-B*1502 before initiating treatment due to association with a risk of developing Stevens–Johnson syndrome.

- HLA-A*3101 in Europeans and Japanese is associated with an increased risk of cutaneous drug reactions such as Stevens–Johnson syndrome and DRESS. Screening is not yet recommended.
- The SmPC recommends LFTs should be performed before initiating treatment and periodically thereafter, particularly in patients with a history of liver disease and elderly patients. Carbamazepine should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.
- It can cause altered LFTs such as elevations in GGT and ALP. In the absence of other signs or symptoms, carbamazepine does not need withdrawing.
- Carbamazepine has weak anticholinergic activity. It may precipitate confusion or agitation in the elderly, or precipitate glaucoma. Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Patients should be monitored for signs of suicidal ideation since anti-epileptic drugs have been associated with this behaviour.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: altered LFTs (raised GGT due to enzyme induction); ataxia; dizziness; drowsiness; fatigue; leucopenia; nausea; urticaria; vomiting.
- *Common*: altered LFTs (raised ALP due to enzyme induction); dry mouth; eosinophilia; headache; hyponatraemia (SIADH); irritation (suppository); oedema; thrombocytopenia; visual disturbances (e.g. blurred vision, diplopia); weight increase.
- *Uncommon*: constipation; diarrhoea; dystonia; exfoliative dermatitis; nystagmus; tremor.
- *Rare*: abdominal pain; agitation; aggression; decreased appetite; confusional state; delayed multi-organ hypersensitivity disorder*; depression; dyskinesia; folate deficiency; hallucinations (visual or auditory); hepatitis; hypertension; hypotension; jaundice; leucocytosis; lymphadenopathy; muscle weakness; paraesthesia; peripheral neuropathy; pruritus; restlessness; SLE; vanishing bile duct syndrome.
- *Very rare*: acne; agranulocytosis; alopecia; anaemia (aplastic, haemolytic, megaloblastic); anaphylactic reaction; arrhythmia; aseptic meningitis; atrioventricular block with syncope; bradycardia; conjunctivitis; aggravated coronary artery disease; dysgeusia; galactorrhoea;

* A delayed hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) may occur at any time during treatment with symptoms such as abnormal LFTs, arthralgia, fever, rashes, vasculitis. If such reactions do occur, carbamazepine should be withdrawn immediately and permanently.

glossitis; gynaecomastia; hearing disorders; hepatic failure; hirsutism; hypercholesterolaemia; hyperhidrosis; hyperprolactinaemia; neuroleptic malignant syndrome; pancreatitis; pancytopenia; photosensitivity; psychosis; pulmonary hypersensitivity; purpura; reticulocytosis; sexual dysfunction (erectile dysfunction; abnormal spermatogenesis); Stevens–Johnson syndrome; stomatitis; thromboembolism; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized by CYP3A4; it is a strong inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and UGT enzymes. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index. Carbamazepine may lower the plasma concentration, diminish, or even abolish the activity of many drugs through enzyme induction.
- *Alfentanil*—risk of reduced analgesic benefit.
- *Celecoxib*—effect of celecoxib may be reduced.
- *Ciprofloxacin*—risk of carbamazepine toxicity through CYP3A4 inhibition.
- *Clonazepam*—effect of clonazepam may be reduced.
- *Codeine*—possible reduced analgesic effect (due to CYP3A4/UGT induction).
- *Corticosteroids*—effect of corticosteroids reduced; higher doses necessary (possibly double or more).
- *Duloxetine*—effect of duloxetine may be reduced due to increased metabolism.
- *Fentanyl*—risk of reduced analgesic benefit.
- *Fluconazole*—possible risk of carbamazepine toxicity.
- *Haloperidol*—effect of haloperidol reduced.
- *Levothyroxine*—increased metabolism may precipitate hypothyroidism.
- *Macrolides*—risk of carbamazepine toxicity (avoid combination or monitor closely) with clarithromycin/erythromycin.
- *Metoclopramide*—theoretical risk of neurotoxicity due to possible increased rate of absorption of carbamazepine.
- *Mirtazapine*—effect of mirtazapine may be reduced.
- *Modafinil*—effect of modafinil may be reduced.
- *Oxycodone*—possible risk of reduced analgesic benefit.
- *Paracetamol*—may increase the risk of hepatotoxicity of paracetamol with long-term co-administration.
- *Rifampicin*—effect of carbamazepine may be reduced.
- *Tramadol*—reduced analgesic effect.
- Avoid excessive amounts of grapefruit juice as it may increase the bioavailability of carbamazepine through inhibition of intestinal CYP3A4.

Pharmacodynamic
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antipsychotics*—lowered seizure threshold.
- *Antidepressants*—lowered seizure threshold.
- *CNS depressants*—risk of excessive sedation.
- *MAOIs*—avoid concurrent use.
- *SSRIs*—potential risk of serotonin syndrome.
- *Tramadol*—lowered seizure threshold.

Dose

Carbamazepine induces its own metabolism after several days. Always start with a low dose and increase gradually by increments of 100mg to 200mg every 2 weeks.

All indications
- Initial dose 100mg to 200mg PO OD or BD (using standard-release or modified-release formulation).
- Increase dose gradually until response is obtained (usually 400mg to 600mg PO BD).
- Alternatively, 125mg to 250mg PR OD or BD. The recommended maximum duration of treatment via the rectal route is 7 days; the recommended maximum dose is 250mg PR QDS.

Dose adjustments

Elderly
- No specific guidance available. Use with caution due to the potential risk of drug interactions. Carbamazepine has anticholinergic activity and the elderly have been shown to be at increased risk of cognitive decline and dementia with such drugs.

Hepatic/renal impairment
- No specific guidance available.
- The SmPC advises caution in hepatic impairment; lower doses may be necessary.
- Normal doses can be used in renal impairment.

Additional information

- Standard-release oral formulations can be taken TDS to QDS if necessary, to reduce the risk of adverse effects. Alternatively, the modified-release formulation can be used.
- Carbamazepine standard-release tablets can be dispersed in water prior to use if necessary.
- Therapeutic plasma concentration range: 4 to 12 micrograms/mL, or 17 to 50micromol/L. Plasma samples are taken immediately prior to the next dose (at steady state).

Pharmacology

Carbamazepine is structurally related to TCA. The mechanism of action is believed to be mediated by blockade of use-dependent Na^+ channels. It has a range of other pharmacological properties, including anticholinergic,

antidiuretic, muscle relaxant and antidepressant actions. Carbamazepine is well absorbed after oral administration (>85%) and is extensively metabolized by CYP3A4; it is a potent inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4. Many drugs are affected (see *Drug interactions*, p. 156).

Reference

1. Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014;**4**:CD005451.

Carbocisteine

Mucodyne® (POM)
Capsule: 375mg (120).
Syrup: 250mg/5mL (300mL).

Generic (POM)
Capsule: 375mg (120).
Oral solution: 250mg/5mL (300mL).
Oral solution sachets (sugar-free): 750mg/10mL (15).

Indications

- Reduction of sputum viscosity (e.g. for use in COPD).

Contraindications and cautions

- Contraindicated for use in active peptic ulceration.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Rare*: anaphylaxis; GI bleeding; skin rashes.
- *Unknown*: erythema multiforme; Stevens–Johnson syndrome; vomiting.

Drug interactions

Pharmacokinetic

- None known.

Pharmacodynamic

- None known.

Dose

- Initial dose 750mg PO TDS, reducing to 750mg PO BD when a satisfactory reduction in cough and sputum production is evident.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- No specific guidance available.

Pharmacology

Carbocisteine affects the nature and amount of mucus glycoprotein, which is secreted by the respiratory tract, reducing the viscosity and allowing easier expectoration.

Celecoxib

Celebrex® (POM)
Capsule: 100mg (60); 200mg (30).

Generic (POM)
Capsule: 100mg (60); 200mg (30).

Indications

- Symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.
- †Pain associated with cancer.[1,2]

Contraindications and cautions

- Celecoxib is contraindicated for use in patients with:
  - active GI bleeding or GI ulceration
  - congestive heart failure (NYHA classes II–IV)
  - established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease
  - hypersensitivity reactions (e.g. asthma, nasal polyps, rhinitis) to ibuprofen, aspirin, or other NSAIDs (including COX-2 inhibitors)
  - hypersensitivity to sulphonamides
  - inflammatory bowel disease
  - severe hepatic dysfunction (serum albumin <25g/L or Child–Pugh score ≥10)
  - severe renal impairment (estimated CrCl <30mL/min).
- Use the minimum effective dose for the shortest duration necessary in order to reduce the risk of cardiac and GI events. Treatment should be reviewed after *2 weeks*. In the absence of benefit, other options should be considered.
- Elderly patients are more at risk of developing adverse effects (see *Dose adjustments*, p. 162).
- Use with caution in the following circumstances:
  - concurrent use of diuretics, corticosteroids, and NSAIDs (see *Drug interactions*, p. 161)
  - congestive heart failure and/or left ventricular dysfunction
  - diabetes mellitus (risk factor for CV adverse effects)
  - hepatic impairment
  - hyperlipidaemia
  - hypertension (particularly uncontrolled)
  - oedema
  - renal impairment
  - smoking (risk factor for CV and GI toxicity).
- Before initiating longer-term treatment, risk factors for CV disease should be considered (e.g. diabetes mellitus, hyperlipidaemia, hypertension, smoking).
- The SmPC recommends monitoring of BP and renal function in patients at risk of CV adverse effects during the initiation of therapy.
- Patients known to be CYP2C9 poor metabolizers should be treated with caution because there is an increased risk of adverse effects;

similarly, drugs that inhibit CYP2C9 should be used with caution (see ➔ *Drug interactions*). In both cases, the prescriber should consider reducing the dose to half the lowest recommended dose.
- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of celecoxib. Patients appear to be at highest risk within the first month of treatment. Patients with a history of sulphonamide allergy may be at greater risk of serious skin reactions or hypersensitivity reactions. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with celecoxib must not be restarted.
- Celecoxib may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Consider co-prescription of misoprostol, a PPI, or an H_2 antagonist (usually reserved if a PPI is not possible) if at high risk of NSAID-induced GI toxicity, e.g. long-term NSAID therapy, concurrent use of drugs that increase the risk of GI toxicity (see ➔ *Drug interactions*).
- Refer to ➔ Chapter 2, *Selection of an NSAID*, p. 49 for further information about selecting an NSAID.
- Celecoxib may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: hypertension (at doses ≥ 400mg daily).
- *Common*: abdominal pain; aggravated allergy; angina pectoris (at doses ≥ 400mg daily); benign prostatic hyperplasia (at doses ≥ 400mg daily); cough; diarrhoea; dizziness; dyspepsia; flu-like symptoms; fluid retention; insomnia; hypertonia; myocardial infarction (at doses ≥ 400mg daily); peripheral oedema; pharyngitis; rash; sinusitis; upper respiratory tract infection; urinary tract infection.
- *Uncommon*: anaemia; anxiety; blurred vision; constipation; CVA; depression; drowsiness; gastritis; heart failure; hyperkalaemia; aggravated hypertension; leg cramps; palpitations; paraesthesia; stomatitis; tachycardia; tinnitus.
- *Rare*: alopecia; ataxia; confusion; GI ulceration; leucopenia; increased LFTs; melaena; oesophagitis; pancreatitis; photosensitivity; taste disturbance; thrombocytopenia.
- *Unknown*: acute renal failure; ageusia; anaphylaxis; anosmia; arrhythmia; arthralgia; bronchospasm; conjunctivitis; DRESS; GI haemorrhage; hallucinations; headache; hepatic failure; hyponatraemia; intracranial haemorrhage; jaundice; ocular haemorrhage; pancytopenia; pulmonary embolism; Stevens–Johnson syndrome; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Celecoxib is metabolized mainly by CYP2C9, with a minor pathway involving CYP3A4; it is also a moderate inhibitor of CYP2D6. *In vitro* data show that celecoxib is a moderate inhibitor of CYP2C19. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Carbamazepine*—can reduce the effectiveness of celecoxib.
- *Clopidogrel*—antiplatelet action may be reduced.
- *Citalopram*—possible increased plasma levels of citalopram (CYP2C19 inhibition).
- *Codeine*—possibly reduced analgesic benefit.
- *Digoxin*—monitoring of serum digoxin is recommended.
- *Fluconazole*—use half of recommended doses of celecoxib as plasma concentration increased.
- *Haloperidol*—celecoxib may inhibit metabolism; possible increased risk of adverse effects.
- *Lithium*—celecoxib may reduce lithium renal excretion.
- *Miconazole*—may increase the effectiveness of celecoxib and risk of adverse effects.
- *Rifampicin*—can reduce the effectiveness of celecoxib.
- *Risperidone*—celecoxib may inhibit metabolism; possible increased risk of adverse effects.
- *Tamoxifen*—celecoxib may reduce metabolism, and therefore effectiveness.
- *Tramadol*—possibly reduced analgesic benefit.

Pharmacodynamic

- *ACE-Is/ARBs*—risk of AKI.
- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—reduced antihypertensive effect.
- *Antiplatelet drugs*—increased risk of GI ulceration or other GI complications.
- *Corticosteroids*—increased risk of GI toxicity.
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Digoxin*—NSAIDs may exacerbate cardiac failure.
- *Diuretics*—increased risk of acute renal insufficiency (potential dehydration and/or hypovolaemia).
- *SSRIs*—increased risk of GI bleeding.
- *Trimethoprim*—increased risk of hyperkalaemia.

Dose

Ensure gastroprotection (e.g. PPI) is prescribed for patients at risk of NSAID-induced GI toxicity.

Celecoxib should be given at a 50% dose reduction to patients who are known or suspected to be CYP2C9 poor metabolizers due to the increased risk of dose-dependent adverse effects.

All indications

- Initial dose 100mg PO BD or 200mg PO OD. Increase, if necessary, to 200mg PO BD. Note the majority of adverse effects are dose-dependent.
- If no benefit after *2 weeks*, discontinue treatment and review.

Dose adjustments

Elderly

- Usual adult doses recommended. Note that the elderly are particularly susceptible to adverse effects. Use the lowest effective dose and for the shortest duration possible.

Hepatic/renal impairment

- In patients with established moderate hepatic impairment with a serum albumin of 25 to 35g/L, an initial dose of 100mg PO OM is suggested. Use of celecoxib in patients with severe hepatic dysfunction is contraindicated (serum albumin <25g/L).
- No specific guidance is available for use in mild to moderate renal impairment. The elderly and those with pre-existing impaired renal function, cardiac failure, or hepatic impairment (due to reliance on the compensatory actions of prostaglandins on renal perfusion) are at greatest risk of renal toxicity. Use the lowest effective dose and for the shortest duration possible. Close monitoring of renal function is recommended. Use of celecoxib in severe renal impairment, however, is contraindicated.

Additional information

- Contents of the capsule can be dispersed in water or fruit juice, or sprinkled on soft food (e.g. yoghurt), if necessary, prior to administration.
- Despite contraindication, several studies have shown that celecoxib can be used safely in patients with aspirin/NSAID sensitivity. There is, however, a risk of cross-sensitivity. If celecoxib is to be used, it should be under close monitoring.[3]

Pharmacology

Like traditional NSAIDs, the mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAIDs, however, celecoxib is a selective, non-competitive inhibitor of COX-2. Celecoxib is mainly eliminated by metabolism, with <1% of the dose being excreted unchanged in urine. Celecoxib metabolism is primarily mediated via CYP2C9 to form three inactive metabolites.

References

1. Derry S, Wiffen PJ, Moore RA, *et al*. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database Syst Rev*. 2017;**7**:CD012638.
2. Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. *Br J Anaesth*. 2019;**123**(2):e412–23.
3. Knowles SR, Drucker AM, Weber EA, Shear NH. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity. *Ann Pharmacother*. 2007;**41**(7):1191–200.

Citalopram ♥

Cipramil® (POM)
Tablet: 10mg (28); 20mg (28); 40mg (28).
Oral drops (sugar-free): 40mg/mL (15mL) (see ➔ *Dose*, p. 168).

Generic (POM)
Tablet: 10mg (28); 20mg (28); 40mg (28).
Oral drops (sugar-free): 40mg/mL (15mL) (see ➔ *Dose*, p. 168).

Indications

- Depression.
- Panic.
- †Agitation associated with dementia.[1,2]

Contraindications and cautions

- Do not use with an irreversible MAOI or within 14 days of stopping one. At least 7 days should elapse after discontinuing citalopram treatment before starting a MAOI.
- Combination with *linezolid* should be avoided unless there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- Although the combination of the MAO-B selective inhibitors *rasagiline* and *selegiline* with SSRIs is well tolerated, there have been case reports of serotonin syndrome. If such a combination is necessary, the recommendation is to use *citalopram* or *sertraline* without exceeding recommended doses.[3] The SmPC states that the dose of selegiline should not exceed 10mg PO OD.
- There is a *known* risk of QT prolongation/TdP with citalopram:
  - do not prescribe for patients taking drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 167)
  - do not prescribe for patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - do not use doses above 40mg (or 20mg in the elderly) unless recommended by a specialist
  - use with caution in patients with significant bradycardia and those with recent acute myocardial infarction or uncompensated heart failure.
- Serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) has been reported in patients using SSRIs. Citalopram should be discontinued immediately if this is suspected and supportive symptomatic treatment should be initiated. Citalopram should not be used concomitantly with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 167).
- Use with caution in epilepsy. SSRIs are, however, considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.

- In addition, use with caution in:
  - diabetes (SSRIs can alter glycaemic control and may cause impaired awareness of hypoglycaemia)
  - elderly (greater risk of hyponatraemia)
  - hepatic/renal impairment (see *Dose adjustments*, p. 169)
  - glaucoma (may cause mydriasis).
- The SmPC makes a specific recommendation about CYP2C19 poor metabolizers (see *Dose adjustments*, p. 169). Note that development of adverse effects is not a predictor of genetic status.
- Akathisia/psychomotor restlessness may occur within the first few weeks of treatment (consider discontinuing).
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Citalopram may increase the risk of haemorrhage. Serotonin is involved in platelet aggregation and haemostasis. Platelets lack the ability to synthesize serotonin and thus rely upon the SERT to obtain it from plasma. SSRIs can inhibit this process. For this reason, citalopram should be used with caution in patients with bleeding disorders or concurrent use with other drugs carrying a similar risk (see *Drug interactions*, p. 167).
- Some patients may experience increased anxiety symptoms at the beginning of treatment. This paradoxical reaction usually subsides within 2 weeks during continued treatment. A low starting dose is advised to reduce the likelihood of this effect.
- There is an increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs. The mechanism is unknown.
- Avoid abrupt withdrawal as symptoms such as agitation, anxiety, dizziness, nausea, sleep disturbance (e.g. insomnia, intense dreams), and tremor can occur. Although generally mild, they can be severe in some patients. Withdrawal symptoms usually occur within the first few days of discontinuing treatment and they usually resolve within 2 weeks, though they can persist in some patients for up to 3 months or longer. See Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: asthenia; drowsiness; dry mouth; headache; insomnia; nausea; sleep disorder; sweating.
- *Common*: abdominal pain; agitation; amnesia; anxiety; apathy; decreased appetite; arthralgia; impaired concentration; confusion; constipation; diarrhoea; dizziness; abnormal dreams; dyspepsia; fatigue; flatulence; migraine; myalgia; palpitations; paraesthesia; pruritus; rhinitis; increased

salivation; sexual dysfunction (*ejaculation failure*, *impotence*, *decreased libido*); tinnitus; tremor; vomiting; weight loss; yawning.
- *Uncommon*: aggression; increased appetite; alopecia; bradycardia; depersonalization; euphoria; hallucinations; mania; menorrhagia; mydriasis (*may lead to glaucoma*); oedema; rash; photosensitivity; sexual dysfunction (*increased libido*); syncope; tachycardia; urinary retention; urticaria; increased weight.
- *Rare*: convulsions; cough; dysgeusia; dyskinesia; haemorrhage (e.g. epistaxis, GI); hepatitis; hyponatraemia; malaise; pyrexia.
- *Unknown*: bone fractures (*increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs*); bruxism; ecchymosis; extrapyramidal reactions; galactorrhoea; hypersensitivity reactions; hypokalaemia; panic attack; priapism; QT prolongation/TdP (*associated predominantly in female patients, with hypokalaemia or with pre-existing cardiac conditions*); serotonin syndrome; SIADH; suicidal behaviour; thrombocytopenia; visual disturbance.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Citalopram is a substrate of CYP2C19, CYP2D6, and CYP3A4; if one pathway is inhibited, metabolism should be compensated for by the other pathways. Nonetheless, inhibitory interactions may still occur if multiple pathways are affected and/or the patient has a 'poor metabolizer' genotype. Escitalopram (the active enantiomer of citalopram) is a weak inhibitor of CYP2D6 and may be considered a weak inhibitor of CYP1A2 and CYP2C19. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.
- Be mindful of CYP2D6 inhibition when switching antidepressants (see ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74).
- *Esomeprazole*—plasma concentration of citalopram may be increased through inhibition of CYP2C19.
- *Fluconazole*—serotonin syndrome has been reported with this combination (also see QT below).
- *Lansoprazole*—plasma concentration of citalopram may be increased through inhibition of CYP2C19.
- *Omeprazole*—plasma concentration of citalopram may be increased through inhibition of CYP2C19.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of citalopram through inhibition of intestinal CYP3A4.

Pharmacodynamic
- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 165)

  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *tapentadol*, *TCAs*, *tramadol*, *trazodone*.
- Citalopram is associated with a known risk of prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see *Contraindications and cautions*, p. 165).
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.
- *Antidiabetics*—SSRIs may alter glycaemic control; risk of impaired awareness of hypoglycaemia.
- *Carbamazepine*—increased risk of hyponatraemia and serotonin syndrome.
- *Cyproheptadine*—may inhibit the effects of SSRIs.
- *Diuretics*—increased risk of hyponatraemia.
- *Lithium*—may enhance the effect of SSRIs.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).
- *NSAIDs*—increased risk of GI bleeding (potentially worse with aspirin and naproxen).
- *SNRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

NB—8mg (four drops) Cipramil® oral drops can be considered equivalent in therapeutic effect to 10mg citalopram tablet. The drops should be mixed with water, orange juice, or apple juice before taking.

Depression

- Initial dose:
  - tablets: 20mg PO OD. The dose should be reviewed after 3–4 weeks and increased, if necessary, to a maximum of 40mg PO OD
  - oral drops: 16mg PO OD (eight drops). The dose should be reviewed after 3–4 weeks and increased, if necessary, in 16mg increments to a maximum of 32mg PO OD (16 drops).

Panic

- Initial dose:
  - tablets—10mg PO OD for the first 7 days, before increasing to 20mg PO OD. The dose can be increased in 10mg increments, as necessary, to the recommended maximum dose of 40mg PO OD
  - oral drops—8mg PO OD (four drops) for the first 7 days, before increasing to 16mg PO OD (eight drops). The dose can be increased in 8mg increments, as necessary, to the recommended maximum dose of 32mg PO OD (16 drops).

[+]Agitation associated with dementia

- Initial dose:
  - tablets—10mg PO OD for the first 7 days, before increasing to 20mg PO OD. The dose can be increased in 10mg increments, as necessary, to the recommended maximum dose of 30mg PO OD
  - oral drops—8mg PO OD (four drops) for the first 7 days, before increasing to 16mg PO OD (eight drops). The dose can be increased in 8mg increments, as necessary, to the recommended maximum dose of 24mg PO OD (16 drops).

Dose adjustments

Elderly

- The manufacturer recommends using half of the recommended dose in the elderly, with a maximum dose of 20mg PO OD (or 16mg oral drops) in patients over 65 years of age.

Hepatic/renal impairment

- Patients with mild to moderate hepatic impairment, or those known to be poor CYP2C19 metabolizers, should have an initial dose of 10mg PO OD for the first 2 weeks of treatment. The dose can be increased to a maximum of 20mg PO OD, if necessary. In severe hepatic impairment, the manufacturer recommends caution and 'extra careful' dose titration. SSRIs can increase the risk of GI bleeding from varices.
- In mild or moderate renal impairment, no dosage adjustment is necessary. Information is unavailable for severe renal impairment (CrCl <30mL/min), so it should be used with caution.

Additional information

- Response in depression may be evident within the first week of treatment; generally, an effect is seen after at least 2 weeks of treatment but may take up to 4 weeks.
- Symptoms of anxiety or panic may worsen on initial therapy. This can be minimized by using lower starting doses. Maximum effectiveness is reached after about 3 months.
- If withdrawal symptoms emerge during discontinuation, increase the dose to prevent symptoms and then start to withdrawal more slowly.
- Despite mixed results in clinical trials, citalopram may be useful in the management of agitation associated with dementia.
- If used for longer than 6 weeks, most antidepressants can cause withdrawal symptoms if they are stopped or rapidly reduced.

Pharmacology

Citalopram is a racemic mixture of R- and S-citalopram (escitalopram). Racemic citalopram is a highly selective inhibitor of SERT, with only very minimal effects on noradrenaline and dopamine neuronal reuptake. It has no or very low affinity for opioid, serotonergic ($5\text{-}HT_{1-7}$), muscarinic (ACh_{m1-5}), α-adrenergic (α_{1-2}), β-adrenergic, dopamine (D_{1-5}), histamine (H_{1-3}), and benzodiazepine receptors. Citalopram is metabolized by CYP2C19, CYP2D6, and CYP3A4 to weaker active metabolites and these

are unlikely to contribute to the overall antidepressant effect. Citalopram is excreted mainly via the liver, with <20% via the kidneys.

References

1. Schneider LS, Frangakis C, Drye LT, *et al*. Heterogeneity of treatment response to citalopram for patients with Alzheimer's disease with aggression or agitation: the CitAD randomized clinical trial. *Am J Psychiatry*. 2016;**173**(5):465–72.
2. Kongpakwattana K, Sawangjit R, Tawankanjanachot I, Bell JS, Hilmer SN, Chaiyakunapruk N. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. *Br J Clin Pharmacol*. 2018;**84**(7):1445–56.
3. Aboukarr A, Giudice M. Interaction between monoamine oxidase B inhibitors and selective serotonin reuptake inhibitors. *Can J Hosp Pharm*. 2018;**71**(3):196–207.

Clonazepam

Generic (CD4a)
Tablet: 500 micrograms (100); 2mg (100).
Liquid: 500 micrograms/5mL (150mL); 2mg/5mL (150mL); *review each SmPC for administration via PVC feeding tubes*.

Unlicensed (CD4a)
Injection: 1mg/mL with 1mL of WFI (10) (see ➔ *Additional information*, p. 173).
Oral drops: 2.5mg/mL (10mL).

Indications

- Epilepsy.
- Myoclonus.
- †Neuropathic pain.[1]
- †Panic/anxiety.[2]
- †Rapid eye movement sleep behaviour disorder.[3]
- †Restless legs syndrome.[4]
- †Terminal restlessness.[5]

Contraindications and cautions

- Contraindicated for use in patients with:
  - acute pulmonary insufficiency
  - myasthenia gravis (may contribute to muscle weakness)
  - severe hepatic impairment
  - severe respiratory insufficiency
  - sleep apnoea syndrome.
- Clonazepam should be used with caution in patients with chronic respiratory disease, renal impairment, or moderate hepatic impairment.
- Following a report of death by respiratory arrest with clonazepam and *methadone*, among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[6] The SmPC warns that concurrent use of clonazepam and opioids increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Suicidal ideation and behaviour have been reported with anti-epileptics.
- Dose reductions may be necessary in the elderly (see ➔ *Dose adjustments*, p. 173).
- Avoid abrupt withdrawal, even if short-duration treatment. In epileptic patients, status epilepticus may be precipitated. In addition, prolonged use of benzodiazepines may result in the development of dependence, with subsequent withdrawal symptoms on cessation of use, e.g. agitation, anxiety, confusion, headaches, restlessness, sleep disturbances, sweating, tremor. The risk of dependence increases with dose and duration of treatment. Gradual withdrawal is advised.

- Clonazepam may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- anterograde amnesia; ataxia; impaired concentration; confusional state; coordination disturbances; diplopia; disorientation; dizziness; drowsiness; erectile dysfunction; fatigue; headache; light-headedness; muscle weakness; nystagmus; paradoxical reactions (aggression, agitation, anxiety, excitability, nervousness, nightmares, vivid dreams); restlessness.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Clonazepam is a major substrate of CYP3A4/5. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of clonazepam through inhibition of intestinal CYP3A4.

Pharmacodynamic

- *Alcohol*—may precipitate seizures.
- *Antidepressants*—reduced seizure threshold.
- *Antipsychotics*—reduced seizure threshold.
- *CNS depressants*—additive sedative effect.
- *Opioids*—see ➔ *Contraindications and cautions*, p. 171.

Dose

The mean absolute oral bioavailability of clonazepam has been shown to be 90%; for CSCI administration, the same dose as for oral administration is recommended, but the prescriber should be alert to the possibility of a less predictable response due to sorption in the PVC infusion set (see ➔ *Additional information*, p. 173).

Epilepsy/myoclonus/[+]neuropathic pain

- Initial dose 1mg PO ON, increased as necessary up to 8mg PO daily in 2–4 divided doses.
- [+]If appropriate, 0.5mg to 4mg via CSCI every 24 hours (but see ➔ *Additional information*, p. 173); higher doses may be necessary.

[+]Panic/anxiety

- Initial dose 0.5mg PO ON, increased as necessary up to 2mg PO ON.
- If appropriate, 0.5mg via CSCI every 24 hours, increased as necessary to a usual maximum of 2mg; higher doses may be required (but see ➔ *Additional information*, p. 173).

+Rapid eye movement sleep behaviour disorder

- Initial dose 0.5mg PO 30 minutes before bedtime, increased as necessary to a maximum dose of 4mg.

+Restless legs syndrome

- Initial dose 0.5mg PO ON, increased as necessary to 2mg PO ON.
- If appropriate, 0.5mg via CSCI every 24 hours, increased as necessary to a usual maximum dose of 2mg (but see ➔ *Additional information*).

+Terminal restlessness

- 1mg to 4mg via CSCI every 24 hours (but see ➔ *Additional information*); higher doses may be necessary.

Dose adjustments

Elderly

- No specific dose reductions stated, but initial doses should not exceed 1mg PO daily.

Hepatic/renal impairment

- No specific guidance available. The dosage of clonazepam must be carefully adjusted to individual requirements.

Additional information

- Clonazepam tablets disperse in water after a short period of time. The tablets (and oral drops) may be administered sublingually.
- The injection formulation is unavailable in the UK but is available to import.
- The 1mg/mL injection of clonazepam must be diluted with the supplied WFI prior to parenteral administration. However, if clonazepam is to be administered via CSCI, this is not necessary.
- Clonazepam may adsorb to PVC. The clinical significance remains unknown, but the SmPC recommends the use of non-PVC equipment for infusions (also refer to the SmPC for oral solutions).
- The mean absolute oral bioavailability of clonazepam has been shown to be 90%, while the IM value is 93%.[7] For CSCI administration, the same dose as for oral administration is recommended, but the prescriber should be alert for the possibility of a less predictable response due to sorption into the PVC infusion set.
- The SmPC states that the stability of diluted parenteral clonazepam is maintained for up to 12 hours. While CSCIs of clonazepam have been administered over 24 hours without apparent unexpected effect, prescribers should consider the use of 12-hourly infusions until further data become available.
- Clonazepam is *physically* compatible under stated conditions with alfentanil, dexamethasone, glycopyrronium, haloperidol, methadone, metoclopramide, morphine sulfate, and oxycodone.[8]

➔ Pharmacology

The exact mechanism of action is unknown, but clonazepam is believed to act as a modulator of the $GABA_A$ receptor, thereby enhancing GABA-ergic transmission in the CNS. It is extensively metabolized by CYP3A4/5 to

7-amino-clonazepam, which is further acetylated by N-acetyl transferase 2 (NAT2). The metabolite 7-amino-clonazepam may have pharmacological actions, potentially competing with clonazepam for the $GABA_A$ receptor. A patient's NAT2 genotype (e.g. slow acetylator) can influence the effect of clonazepam.

References

1. Hugel H, Ellershaw JE, Dickman A. Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain. *J Pain Symptom Manage*. 2003;**26**(6):1073–4.
2. Freire RC, Amrein R, Mochcovitch MD, *et al*. A 6-year posttreatment follow-up of panic disorder patients: treatment with clonazepam predicts lower recurrence than treatment with paroxetine. *J Clin Psychopharmacol*. 2017;**37**(4):429–34.
3. Aurora RN, Zak RS, Maganti RK, *et al*. Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J Clin Sleep Med*. 2010;**6**(1):85–95.
4. Comella CL. Treatment of restless legs syndrome. *Neurotherapeutics*. 2014;**11**(1):177–87.
5. Burke AL. Palliative care: an update on 'terminal restlessness'. *Med J Aust*. 1997;**166**(1):39–42.
6. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
7. Crevoisier C, Delisle MC, Joseph I, Foletti G. Comparative single-dose pharmacokinetics of clonazepam following intravenous, intramuscular and oral administration to healthy volunteers. *Eur Neurol.* 2003;**49**(3):173–7.
8. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Co-danthramer

Co-danthramer (generic—POM)
Suspension: 25/200 in 5mL, dantron 25mg, poloxamer '188' 200mg/5mL (300mL); 75/1000 in 5mL, dantron 75mg, poloxamer '188' 1g/5mL (300mL).

Indications

- Treatment of constipation in terminally ill patients.

Contraindications and cautions

- Contraindicated in intestinal obstruction.
- Avoid in patients with abdominal pain of unknown origin.
- Use with caution in incontinent patients (both urinary and faecally) due to the risk of irritation and excoriation.
- Use with caution in patients with renal impairment—hypermagnesaemia may occur.
- The suspensions contain 3.17% v/v alcohol.

Adverse effects

- The frequency is not defined, but reported adverse effects include:
  - abdominal cramp; rash; tiredness; weakness.
- Dantron may cause temporary and harmless pink or red colouring of the urine and perianal skin.
- Prolonged contact with the skin can lead to superficial sloughing of the skin (co-danthramer 'burn'). This should be prevented by application of a barrier cream in susceptible patients.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- *Laxatives*—use of a stool softener may enhance the systemic absorption of danthron.

Pharmacodynamic

- *Anticholinergics*—antagonizes the laxative effect.
- *Cyclizine*—antagonizes the laxative effect.
- *Opioids*—antagonizes the laxative effect.
- *5-HT_3 antagonists*—antagonizes the laxative effect.
- *TCAs*—antagonizes the laxative effect.

Dose

- *25/200 in 5mL*: 5mL to 10mL ON. Increase as necessary to maximum of 10mL PO BD+. Consider changing to co-danthramer 'strong' if no response.
- *75/1000 in 5mL*: 5mL ON. Increase as necessary to maximum of 10mL PO BD.+ Review treatment if no response.

Dose adjustments

Elderly

- No specific dose adjustments recommended by the manufacturer.

Hepatic/renal impairment

- No specific dose adjustments recommended by the manufacturer.

Additional information

- Warn patients that the urine may be coloured red/orange.

Pharmacology

Co-danthramer consists of dantron poloxamer 188. Dantron is an anthraquinone derivative chemically related to the active principle of cascara and senna. It is believed to stimulate muscles of the large intestine through action on the myenteric plexus. Griping should not occur, as the small intestine is not affected. Poloxamer 188 is a surfactant that improves the penetration of water into faecal material, and it also has a lubricant effect.

Codeine

Generic (CD5 POM)
Tablet: 15mg (28; 30; 100; 500); 30mg (28; 30; 100; 500); 60mg (28).
Oral solution: 25mg/5mL (500mL).
Linctus: 15mg/5mL (200mL; 2000mL). (*NB—sugar-free linctus is available*.)
Injection (CD2 POM): 60mg/mL (10).

Combination products

Certain products containing <15mg of codeine and paracetamol are available OTC (*CD5 P*).

Co-codamol 8/500
Generic (CD5 POM)
Tablet: codeine phosphate 8mg, paracetamol 500mg (30; 32; 100; 500; 1000).
Capsule: codeine phosphate 8mg, paracetamol 500mg (32; 100).
Effervescent or dispersible tablet: codeine phosphate 8mg, paracetamol 500mg (32; 60; 100).

Co-codamol 15/500
Generic (CD5 POM)
Tablet: codeine phosphate 15mg, paracetamol 500mg (100).
Capsules: codeine phosphate 15mg, paracetamol 500mg (100).
Effervescent tablet: codeine phosphate 15mg, paracetamol 500mg (100).

Co-codamol 30/500
Generic (CD5 POM)
Tablet: codeine phosphate 30mg, paracetamol 500mg (30; 100).
Caplet: codeine phosphate 30mg, paracetamol 500mg (100).
Capsule: codeine phosphate 30mg, paracetamol 500mg (100).
Effervescent or dispersible tablet: codeine phosphate 30mg, paracetamol 500mg (32; 100).

Co-codamol 60/500
Generic (CD5 POM)
Tablet: codeine phosphate 60mg, paracetamol 500mg (100).

Co-codaprin 8/400
Generic (CD5 POM)
Tablet: codeine phosphate 8mg, aspirin 400mg (32).
Dispersible tablet: codeine phosphate 8mg, aspirin 400mg (32; 100).

Indications

- Management of mild to moderate pain.
- Treatment of diarrhoea.
- Cough (linctus).

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in

palliative care, although there may be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation).

- Nonetheless, the SmPC contraindicates the use of codeine in the following instances:
  - acute abdomen
  - acute alcoholism
  - CYP2D6 ultrarapid metabolizers (see below)
  - diarrhoea associated with either pseudomembranous colitis or poisoning
  - head injury (opioids interfere with pupillary observations)
  - obstructive airways disease
  - paralytic ileus
  - raised intracranial pressure
  - respiratory depression.

- Codeine is metabolized by CYP2D6 into morphine, its active metabolite. Ultrarapid metabolizers convert codeine into morphine more rapidly and completely than other people, which can result in higher-than-expected plasma morphine concentrations. Even at usual doses, ultrarapid metabolizers may experience symptoms of overdose such as extreme sleepiness, confusion, or shallow breathing.
- Poor metabolizers or those taking concurrent CYP2D6 inhibitors (see ➔ *Drug interactions*, p. 180) may derive little or no analgesic benefit from codeine. Titration of an alternative opioid is recommended, rather than substitution to an equianalgesic dose (see Box 1.3 for more information).

- Use codeine with caution in the following instances:
  - adrenocortical insufficiency (lower doses recommended)
  - arrhythmias
  - asthma (can release histamine)
  - bowel obstruction
  - concurrent use with CYP2D6 inhibitors (see ➔ *Drug interactions*, p. 180)
  - COPD
  - diseases of the biliary tract (e.g. gallstones)
  - elderly (see ➔ *Dose adjustments*, p. 181)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 181)
  - hypothyroidism (lower doses suggested)
  - inflammatory bowel disease
  - myasthenia gravis
  - pancreatitis
  - raised intracranial pressure
  - renal impairment (see ➔ *Dose adjustments*, p. 181)
  - prostatic hypertrophy
  - sleep apnoea (respiratory effects of opioids are more pronounced during sleep).
- Effervescent formulations contain up to Na^+ 16.9mmol/L (check individual product). Avoid in renal impairment and use with caution in patients with hypertension or congestive heart failure.

- There have been rare case reports of opioid analgesics involved in serotonin toxicity (see Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs, SSRIs, SNRIs, and TCAs (see *Drug interactions*, p. 180). Codeine, like *morphine*, is associated with low risk; nonetheless, treatment must be reviewed urgently if symptoms develop, codeine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone*, among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of codeine and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Avoid abrupt withdrawal as the development of physical and/or psychological dependence can occur within 2 weeks of continual use. An abstinence syndrome may be precipitated if codeine is suddenly discontinued; it may occur within a few hours after withdrawal and is maximal between 1 and 3 days. Withdrawal symptoms include:
  - abdominal colic
  - anxiety
  - body aches
  - diarrhoea
  - dysphoria
  - flu-like symptoms
  - irritability
  - mydriasis
  - nausea
  - restless legs syndrome
  - tachycardia
  - tremors.
- Codeine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).

- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

Adverse effects

The frequency is not defined. Refer to the SmPC for a full list of adverse effects. Commonly reported adverse effects include the following:

- constipation; dizziness; drowsiness; headache; nausea; pruritus; rash; shortness of breath; vomiting.

Less commonly reported adverse effects include:

- abdominal pain; biliary spasm; confusion; decreased libido; dry mouth; flushing; hallucinations; hypotension; paraesthesia; paralytic ileus; respiratory depression; sweating; ureteric spasm; urinary retention; visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Codeine preferentially undergoes glucuronidation via UGT2B4 and UGT2B7. Minor pathways involve CYP3A4 and CYP2D6 (to morphine). Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.
- The efficacy of codeine may be reduced by CYP2D6 inhibitors (such as *duloxetine*, *fluoxetine*, *haloperidol*, *levomepromazine*, *paroxetine*, and *quinine*) or increased by CYP3A4 inducers (e.g. *carbamazepine*, *rifampicin*). The clinical implications of co-administration with these drugs are unknown, and the prescriber should be aware of the potential for altered response.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 177.
- *CNS depressants*—risk of excessive sedation.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of codeine may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOI*—risk of severe and unpredictable interactions with MAOIs, involving the potentiation of opioid or serotonergic effects.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 177.

Dose

Pain

- 30mg to 60mg PO or IM every 4 hours PRN (to a maximum of 240mg daily)
- [+]Alternatively, codeine can be given either 30mg to 60mg SUBCUT every 4 hours PRN (to a maximum dose of 240mg daily) or up to 240mg via CSCI over 24 hours.
- Co-codamol 8/500, 15/500, and 30/500; 1–2 tablets PO every 4 hours (maximum of eight daily due to paracetamol).
- Co-codaprin formulations are not recommended.

Diarrhoea

- 15mg to 60mg PO 4- to 6-hourly.

Cough

- 5mL to 10mL (of linctus) PO TDS to QDS.

Dose adjustments

Elderly

- No specific guidance is available, although lower starting doses may be preferable. Dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance is available, although in patients with hepatic impairment, the plasma concentration is expected to be increased, but the analgesic effect will most likely be reduced. Codeine is generally not recommended and alternative drugs should be considered.
- No specific guidance is available for patients with renal impairment. However, since active metabolites are renally excreted, lower starting doses may be preferable and dose requirements should be individually titrated.

Additional information

- Dihydrocodeine and codeine have traditionally been used, instead of morphine (or alternative), for headache associated with brain metastases. There is no evidence to support this use.
- CYP2D6 poor metabolizers (up to 10% of the Caucasian population) cannot produce morphine, the active metabolite of codeine. Drug interactions can affect the metabolism of codeine via inhibition of CYP2D6. The clinical consequences of genotype and drug interaction are unknown. Genetic variations and drug interactions lead to the possibility of a modified adverse effect profile and varied analgesic response.
- Codeine is included in a number of over-the counter preparations for coughs, colds, and pain, so drug histories must include remedies patients may have self-selected.

Pharmacology

Codeine is a naturally occurring weak opioid agonist derived from opium. By mouth, it is of similar potency to dihydrocodeine; parenterally, it is considered to be half as potent as dihydrocodeine. Oral codeine is

normally regarded as being about one-tenth as potent as oral morphine. Approximately 50–70% of codeine is converted to codeine-6-glucuronide by UGT2B7 (and UGT2B4 to a lesser extent). A further 10–15% is metabolized by CYP3A4 to norcodeine. Both codeine-6-glucuronide and norcodeine have a similar affinity for MOR to codeine. Of more importance is metabolism by CYP2D6 (approximately 10%) to morphine. A percentage of the Caucasian population (5–10%) are poor metabolizers of CYP2D6, so codeine will be less effective, or even ineffective, in this group. Co-administration of CYP2D6 inhibitors produces similar effects. The metabolites are renally excreted.

Reference

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.

Cyclizine

Generic (P)
Tablet (scored): 50mg (100).

Generic (POM)

Injection: 50mg/mL (5).

Unlicensed (POM)

Available on a named-patient basis as manufactured specially.
Oral solution/suspension: 50mg/5mL (100mL).
Suppositories: 12.5mg; 25mg; 50mg; 100mg.

Indications

- Prevention and treatment of nausea and vomiting.

Contraindications and cautions

- Avoid in patients with porphyria.
- Cyclizine should be used with caution in patients with:
  - glaucoma; prostatic hypertrophy
  - severe congestive heart failure.
- The anticholinergic effect of cyclizine can be additive to that of other drugs. Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Cyclizine has been reported to exacerbate idiopathic Parkinson's disease (see ➔ *Adverse effects*). This is believed to be caused by the anticholinergic activity of cyclizine affecting the balance between dopaminergic and cholinergic transmission in the corpus striatum.
- Cyclizine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- blurred vision; confusion; constipation; delirium; drowsiness; dry mouth; extrapyramidal motor disturbances (rare); hallucinations (especially with higher doses); headache; hypersensitivity reactions (rare); nervousness; restlessness; tachycardia; urinary retention.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Currently, there are no recognized pharmacokinetic interactions. Cyclizine, however, is metabolized by CYP2D6 to norcyclizine, a relatively inactive metabolite, with <1% of a dose excreted as unchanged drug in the urine. Co-administration with drugs that are

metabolized by, or affect the activity (induction or inhibition—see *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Anticholinergics*—increased risk of adverse effects.
- *CNS depressants*—increased risk of CNS adverse effects.
- *Domperidone*—may inhibit prokinetic effect.
- *Metoclopramide*—may inhibit prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

Cyclizine has an oral bioavailability of 50% due to high first-pass metabolism. When converting from oral to parenteral cyclizine, it may be prudent to use a conversion of 3:2 to reduce the risks of adverse effects.

- Usual dose 50mg PO or 25mg to 50mg SUBCUT+ BD to TDS PRN. Alternatively, 100mg to 150mg via CSCI+ over 24 hours.
- Maximum daily dose of 200mg+ PO or SUBCUT.

Dose adjustments

Elderly

- The SmPC indicates that the normal adult dosage is appropriate. Note that the elderly may be more susceptible to the central and anticholinergic effects of cyclizine (which may be additive with concomitant drugs); there may be an increased risk of cognitive decline and dementia.

Hepatic/renal impairment

- No specific guidance available. Dose requirements should be individually titrated.
- In hepatic impairment, empirical dose adjustments may be necessary since cyclizine undergoes hepatic clearance.
- Dose reductions may be necessary in renal impairment.

Additional information

- The antiemetic effect should occur within 2 hours of oral administration and lasts approximately 4 hours. Parenteral administration would be expected to produce a much quicker response.
- Cyclizine should be avoided in severe congestive heart failure because it can cause a reduction in cardiac output associated with increases in HR, mean arterial pressure, and pulmonary wedge pressure.
- The tablets can be crushed and dispersed in water; the resulting solution may have a bitter taste.
- Cyclizine injection must be diluted with WFI. It is incompatible with NaCl and in solutions with a pH of 6.8 or more.

- Cyclizine is *chemically and physically* compatible under stated conditions with alfentanil, hydromorphone, morphine sulfate, and oxycodone. Under stated conditions, cyclizine is *physically* compatible with dexamethasone, haloperidol, and midazolam.[1]
- There appear to be concentration-dependent compatibility issues with alfentanil, Buscopan®, dexamethasone, glycopyrronium, hydromorphone, metoclopramide, and oxycodone, although the specific details are unknown.
- Cyclizine and diamorphine mixtures are chemically and physically stable in WFI up to concentrations of 20mg/mL over 24 hours. If the diamorphine concentration exceeds 20mg/mL, crystallization may occur unless the concentration of cyclizine is no greater than 10mg/mL. Similarly, if the concentration of cyclizine exceeds 20mg/mL, crystallization may occur unless the concentration of diamorphine is no greater than 15mg/mL.[1]

Pharmacology

Cyclizine is a histamine H_1 receptor antagonist and has a low incidence of drowsiness. It also possesses anticholinergic activity. The exact mechanism by which cyclizine can prevent or suppress nausea and vomiting from various causes is unknown, but it may have an inhibitory action within part of the midbrain referred to as the vomiting centre. Cyclizine also increases lower oesophageal sphincter tone and reduces the sensitivity of the labyrinthine apparatus. It is metabolized in the liver by CYP2D6 to a relatively inactive metabolite.

Reference

1. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Cyproheptadine

Periactin® (P)
Tablet (scored): 4mg (30).

Indications

- Symptomatic relief of allergy (e.g. hay fever, allergy).
- Vascular headache and migraine.
- †Symptomatic relief of serotonin syndrome (see ➔ Chapter 1, *Serotonin toxicity*, p. 29).
- †Appetite stimulant (other treatments preferred).
- †Management of diarrhoea associated with carcinoid syndrome (octreotide generally preferred).

Contraindications and cautions

- Contraindicated for use in the elderly (see ➔ *Dose adjustments*, p. 187) and patients with:
  - glaucoma
  - pyloroduodenal obstruction
  - predisposition to urinary retention or bladder neck obstruction
  - stenosing peptic ulcer
  - symptomatic prostatic hypertrophy.
- Avoid concurrent use with MAOIs (see ➔ *Drug interactions*, p. 187).
- Use cautiously in patients with:
  - bronchial asthma
  - CV disease
  - hypertension
  - hyperthyroidism
  - increased intraocular pressure.
- The anticholinergic effect of cyproheptadine can be additive to that of other drugs. Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Cyproheptadine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but commonly reported adverse effects include:

- abdominal pain; appetite stimulation; blurred vision; constipation; diarrhoea; dizziness; drowsiness (should improve within 1 week of treatment); dry mouth; fatigue; headache; hypotension; nausea; paradoxical reactions (e.g. aggressive behaviour, excitation, irritability, nervousness, insomnia, restlessness); thickening of bronchial secretions; weight gain.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- The mechanism of hepatic metabolism is unspecified.
- No known pharmacokinetic interactions.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *SSRIs*—antidepressant effect may be reduced by cyproheptadine.
- *CNS depressants*—risk of excessive sedation.
- *MAOIs*—may cause hallucinations.

Dose

Symptomatic relief of allergy

- Initial dose 4mg PO TDS. Dose can be increased to a maximum of 32mg PO daily.

Vascular headache and migraine

- Initial dose 4mg PO, repeated if necessary after 30 minutes. Patients who respond usually obtain relief with 8mg, and this dose should not be exceeded within a 4- to 6-hour period.
- Usual maintenance dose is 4mg PO every 4–6 hours.

†Symptomatic relief of serotonin syndrome

- Most patients will respond to an initial dose of 12mg PO, followed by additional doses of 2mg every 2 hours until a clinical response is seen (suggested maximum daily dose of 32mg). As the patient improves, cyproheptadine can be continued at a dose of 8mg every 6 hours until symptoms resolve.

†Appetite/†carcinoid

- Initial dose 4mg PO TDS. Dose can be to 8mg PO TDS. Further dose increases are unlikely to be of additional benefit.

Dose adjustments

Elderly

- Elderly patients are more likely to experience adverse effects such as dizziness, sedation, and hypotension. The UK manufacturer contraindicates the use of cyproheptadine in elderly patients. However, for treatment of serotonin syndrome, the lowest effective dose should be used.

Hepatic/renal impairment

- No specific guidance available. Dose requirements should be individually titrated.

Additional information

- Tablets can be crushed and dispersed in water prior to administration, if necessary.

Pharmacology

Cyproheptadine is a piperidine antihistamine with weak anticholinergic properties. In addition, it also antagonizes 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 serotonin receptors. This latter effect makes cyproheptadine particularly useful in symptomatic treatment of serotonin syndrome. The drug is extensively metabolized, with the metabolites being excreted renally. The exact mechanism of metabolism is unknown but may involve the cytochrome P450 system.

Cyproterone ♡

Cyprostat® (POM)
Tablet (scored): 50mg (160); 100mg (80).

Generic (POM)
Tablet: 50mg (56); 100mg (84).

Indications

- Prostate cancer:
  - to suppress 'flare' with initial gonadorelin therapy
  - long-term palliative treatment where gonadorelin analogues or orchidectomy are contraindicated or not tolerated, or where oral therapy is preferred
  - treatment of hot flushes in patients receiving gonadorelin therapy or after orchidectomy.

Contraindications and cautions

- Hepatotoxicity has been reported in patients treated with cyproterone acetate >100mg PO daily, usually after several months. LFTs should be performed before and regularly during treatment. If symptoms of hepatotoxicity occur and are believed to be caused by cyproterone, it should normally be withdrawn.

- Cyproterone must not be used in patients with:
  - existing thromboembolic condition
  - liver disease (refer to the SmPC)
  - malignant tumours (except prostate)
  - meningioma or a history of meningioma.
- Use with caution in the following:
  - depression (the condition may deteriorate)
  - diabetes (cyproterone can affect carbohydrate metabolism; also increased risk of thromboembolic events)
  - hepatic impairment (see above)
  - history of CV disease (although not mentioned in the SmPC or the *CredibleMeds®* database, androgen deprivation therapy may prolong the QT interval)
  - history of thromboembolic disease (may recur with cyproterone)
  - sickle cell anaemia.
- Regular blood counts (as well as LFTs) should be performed due to the risk of anaemia.
- Cyproterone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: decreased libido; erectile dysfunction; reduced sexual drive.

- *Common*: depression (usually short term); dyspnoea (mainly at high doses); fatigue; gynaecomastia (reversible); hepatotoxicity (jaundice/hepatitis; usually doses >100mg OD); hot flushes; restlessness (usually short term); sweating; weight gain (long-term treatment).
- *Uncommon*: rash.
- *Rare*: galactorrhoea; hypersensitivity reactions.
- *Unknown*: anaemia (long-term treatment); dry skin; meningioma (long-term treatment); osteoporosis; thromboembolic events.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Cyproterone is metabolized by CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Pharmacodynamic

- Androgen deprivation therapy may prolong the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.

Dose

Suppression of 'flare'

- Initial dose 100mg PO BD after meals for 5–7 days, followed by 100mg PO BD after meals for 3–4 weeks with the LHRH analogue.

Long-term palliative treatment

- 200mg to 300mg PO daily in 2–3 divided doses after meals.

Hot flushes

- Initial dose 50mg PO OD after food, increasing if necessary to 50mg PO BD to TDS after meals.

Dose adjustments

Elderly

- Usual adult doses recommended.

Hepatic/renal impairment

- No specific guidance is available for use in hepatic impairment. The manufacturer contraindicates use in patients with liver disease (refer to the SmPC).
- No specific guidance is available for use in renal impairment, although accumulation is unlikely, given the hepatic clearance of the drug.

Additional information

- Although tablets may be crushed and dispersed in water prior to administration, this is not recommended to be performed due to the risk of exposure.

Pharmacology

Cyproterone is an anti-androgen that antagonizes the actions of testosterone and its metabolite dihydrotestosterone. It also has progestogenic activity, which exerts a negative feedback effect on the hypothalamus, causing a reduction in gonadotrophin release and subsequent diminished production of testicular androgens. Prolactin levels can rise at higher doses. It is completely absorbed orally and undergoes extensive metabolism via various pathways. The main metabolite has similar anti-androgen properties, but little progestogenic activity.

Dalteparin

Fragmin® (POM)

Injection (single-dose syringe for SUBCUT use): 2500 units/0.2mL; 5000 units/0.2mL; 7500 units/0.3mL; 10,000 units/0.4mL; 12,500 units/0.5mL; 15,000 units/0.6mL; 18,000 units/0.72mL syringe.

Injection (for SUBCUT or IV use): 2500 units/mL (4mL ampoule; 10); 10,000 units/mL (1mL ampoule; 10).

Injection (for SUBCUT use): 25,000 units/mL (4mL multi-dose vial).

Injection (graduated 1mL syringe for SUBCUT use): 10,000 units/mL.

Generic (POM)

Injection (single-dose syringe for SUBCUT use): 2500 units/0.2mL; 5000 units/0.2mL; 7500 units/0.3mL; 10,000 units/0.4mL; 12,500 units/0.5mL; 15,000 units/0.6mL; 18,000 units/0.72mL syringe.

Injection (graduated 1mL syringe for SUBCUT use): 10,000 units/mL.

Indications

- Treatment and prophylaxis of DVT and PE.
- Extended treatment of symptomatic VTE and prevention of its recurrence in patients with solid tumours.
- Other indications apply but are not normally relevant in palliative care; refer to the SmPC.

Contraindications and cautions

- Dalteparin is contraindicated for use in:
  - acute gastroduodenal ulcer
  - body weight <40kg at the time of VTE (extended use only, due to lack of data)
  - cerebral haemorrhage (within 3 months, unless due to systemic emboli)
  - current or history of heparin-induced thrombocytopenia
  - haemorrhagic pericardial or pleural effusion
  - known haemorrhagic diathesis or other active haemorrhage
  - septic endocarditis.
- Avoid IM injection of other drugs if daily dose of dalteparin exceeds 5000 units.
- Use with caution in patients with an increased risk of bleeding complications and seek specialist advice if necessary:
  - brain tumours (increased risk of intracranial bleeding)
  - concurrent use of anticoagulant/antiplatelet agents/NSAIDs (see *Drug interactions*, p. 193)
  - diabetes mellitus (increased risk of hyperkalaemia and metabolic acidosis)
  - haemorrhagic stroke
  - hepatic impairment
  - renal impairment
  - retinopathy (hypertensive or diabetic)
  - surgery
  - trauma

  - thrombocytopenia
  - uncontrolled hypertension.
- A baseline platelet count should be taken prior to initiating treatment, and monitored closely during the first 3 weeks (e.g. every 2–4 days) and regularly thereafter.
- Dalteparin must not be administered by IM injection—risk of injection site haematoma.
- Advice should be sought from anaesthetic colleagues if considering an epidural intervention in a patient receiving dalteparin, due to the risk of spinal haematoma.
- LMWH can inhibit aldosterone secretion, which can cause reversible hyperkalaemia. Patients with pre-existing renal impairment are more at risk. Potassium (K^+) should be measured in at-risk patients prior to starting LMWH and monitored regularly thereafter, especially if treatment is prolonged beyond 7 days.
- *Prophylactic doses of dalteparin are not sufficient to prevent valve thrombosis in patients with prosthetic heart valves.*

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: bleeding (from any site); pain at injection site; subcutaneous haematoma at injection site; transient changes to liver transaminase levels—clinical significance unknown; mild reversible thrombocytopenia (usually occurs within first 3 weeks of treatment).
- *Uncommon*: hypersensitivity; pruritus; urticaria.
- *Rare*: alopecia (with prolonged use—usually transient); skin necrosis.
- *Unknown*: anaphylactic reactions; hypoaldosterism; hyperkalaemia; immunologically mediated heparin-induced thrombocytopenia; osteoporosis (long-term treatment); rash.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None recognized.

Pharmacodynamic

- Drugs with anticoagulant or antiplatelet effect may enhance the effect of dalteparin:
  - *aspirin*
  - *clopidogrel*
  - *dipyridamole*
  - *NSAIDs*.
- *ACE-Is*—increased risk of hyperkalaemia.
- *Amiloride*—increased risk of hyperkalaemia.
- *Antihistamines*—possibly reduce anticoagulant effect.
- *Ascorbic acid*—possibly reduces anticoagulant effect.
- *Corticosteroids*—increased risk of GI bleeding.
- *Spironolactone*—increased risk of hyperkalaemia.
- *SSRIs*—increased risk of bleeding.

Dose

Refer to Haematology for advice if platelets are below 75 × 10^9/L or bodyweight <40kg or >150kg.

Treatment of venous thromboembolism

- The adult dose is weight-dependent and administered OD SUBCUT (see Table 3.1).
- Alternatively, a dose of 200 units/kg (maximum 18,000 units) can be given.

Table 3.1 Dalteparin dosage for treatment of DVT and PE

Weight (kg)	Dose (units)
Up to 46	7500
46–56	10,000
57–68	12,500
69–82	15,000
83 and over	18,000

- Patients at high risk of bleeding should have the daily dose divided and administered BD (i.e. 100 units/kg SUBCUT BD).
- Patients usually start oral anticoagulation at the same time and continue both until the INR is within the target range. This generally takes 5 days. However, cancer patients unsuitable for oral anticoagulation may require long-term treatment with LMWH. Treatment is occasionally continued indefinitely.
- [+]Higher doses may be indicated for patients with a body weight of >100kg. Discuss with the local Haematology team.

Extended treatment of venous thromboembolism

- The recommended duration of treatment is 6 months, extended if necessary based on a risk–benefit assessment.
- For the first 30 days of treatment, use the dose schedule as above.
- In the case of chemotherapy-induced thrombocytopenia, the following dose adjustments should be made:
  - platelet counts between 50,000 and 100,000/mm^3—reduce daily dose by 2500 units until the count is ≥100,000mm^3
  - platelet counts <50,000/mm^3—discontinue until the count is >50,000/mm^3.
- For months 2–6, a dose of 150 units/kg (maximum 18,000 units) should be as shown in Table 3.2.
- [+]Higher doses may be indicated for patients with a body weight of >100kg. Discuss with the local Haematology team.

Table 3.2 Extended treatment of VTE

Weight (kg)	Dose (units)
Up to 56	7500
57–68	10,000
69–82	12,500
83–98	15,000
99 and over	18,000

- During the extended phase of treatment (months 2–6), the following dose adjustments should be made in the case of chemotherapy-induced thrombocytopenia:
  - platelet counts <50,000/mm^3—discontinue until the count is >50,000/mm^3
  - platelet counts between 50,000 and 100,000/mm^3—reduce the dose, as shown in Table 3.3, until the count is ≥100,000/mm^3.

Table 3.3 Dose adjustments for low platelet counts

Weight (kg)	Adjusted dose (units)
Up to 56	5000
57–68	7500
69–82	10,000
83–98	12,500
99 and over	15,000

Prophylaxis of deep vein thrombosis

- For medical prophylaxis (including immobile cancer patients)—5000 units SUBCUT OD. The duration of treatment depends upon the risk factors identified (e.g. immobile inpatients may be considered for treatment from admission until discharge). Graduated compression stockings should be considered if LMWH is contraindicated.
- [+]In certain circumstances, a dose reduction to 2500 units SUBCUT OD may be warranted in patients with:
  - <50kg body weight
  - CrCl <30mL/min and minor bleeding.
- [+]Higher doses may be indicated for patients with a body weight of >100kg. Discuss with the local Haematology team.
- For surgical prophylaxis:
  - moderate risk—2500 units SUBCUT before the procedure and each day for 5–7 days or longer (until mobilized)

  - high risk—2500 units SUBCUT before the procedure and 8–12 hours later, then 5000 units SUBCUT OD for 5–7 days or longer (until mobilized).
- ✝Long-distance air travel:
  - cancer patients are at risk of developing VTE during long-distance air travel (considered >6 hours)
  - supply the patient with sufficient quantities to cover flights and provide a cover letter for immigration purposes (see Chapter 2, *Travelling abroad with medicines*, p. 39)
  - 5000 units SUBCUT 2–4 hours prior to the flight. Should there be long-distance connections, only administer another dose if the following flight is >24 hours after the previous dose (e.g. following a stopover).

Dose adjustments

Elderly

- Usual adult doses recommended.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. The SmPC advises caution due to increased risk of bleeding.
- Dosage adjustments in patients with renal impairment *must* be based on CrCl, *not* on eGFR. In the case of significant renal impairment, defined as CrCl <30mL/min, the dose of dalteparin should be adjusted based on anti-factor Xa activity. If the anti-factor Xa level is less or greater than the desired range, the dose of dalteparin should be increased or reduced, respectively, and the anti-factor Xa measurement should be repeated after 3–4 doses. This process should be repeated until the desired anti-factor Xa level is achieved.

Additional information

- Actual body weight and CrCl should be used for dose calculations.
- Measurement of anti-factor Xa levels, in conjunction with the local Haematology department, can help guide the dose of dalteparin in difficult cases.
- Refer to local guidelines for target anti-factor Xa ranges. As an example, for prophylaxis, the target anti-factor Xa range is 0.2–0.4IU/mL. For treatment, the target range is 0.4–0.8IU/mL. Check anti-factor Xa level 3–5 hours post-*third* dose, irrespective of dosing frequency.
- Warfarin may be unsuitable for cancer patients who may require long-term treatment with LMWH. Treatment is occasionally continued indefinitely. Dalteparin is currently unlicensed for extended treatment.
- If switching from dalteparin to warfarin, patients must continue both until the INR is within the target range. This generally takes 5 days.
- When switching from dalteparin to a DOAC, the DOAC should be given 0–2 hours before the time when the next scheduled administration of dalteparin would be due.
- When switching from a DOAC, the first dose of dalteparin should be given at the time when the next DOAC dose would be taken.

- The risk of heparin-induced thrombocytopenia is low with dalteparin but may occur between the fifth and 21st day following initiation. If there is a 30–50% reduction in the platelet count, LMWH should be stopped.

Pharmacology

Dalteparin is an LMWH produced from porcine-derived sodium heparin. It acts mainly through its potentiation of the inhibition of factor Xa and thrombin by antithrombin. Dalteparin is eliminated primarily via the kidneys, hence the need for dose adjustments in renal impairment. Local protocols may help to indicate when treatment of palliative care patients with dalteparin is appropriate.

Demeclocycline

Generic (POM)
Capsule: 150mg (28).
Other strengths and formulations may be available to import. Refer to the *BNF*.

Indications

- Treatment of chronic hyponatraemia associated with SIADH, secondary to malignant disease, where water restriction is ineffective, and in cases where the patient does not have concomitant cirrhosis.

Contraindications and cautions

- Contraindicated for use in patients with acute porphyria.
- Use with caution in patients with liver or renal impairment, or in patients with concurrent use of potentially hepatotoxic or nephrotoxic drugs.
- Care should be taken in patients with myasthenia gravis due to a potential for weak neuromuscular blockade.
- May cause photosensitive skin reactions—warn the patient to avoid direct exposure to sunlight or sunlamps and to discontinue at the first sign of skin discomfort. Demeclocycline is stated to have the greatest risk of all tetracyclines for inducing such reactions.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- blood dyscrasias (e.g. haemolytic anaemia, neutropenia, thrombocytopenia); oral candidosis; diarrhoea; dizziness; dysphagia; headache; hepatitis; nausea; oesophagitis; pancreatitis; photosensitivity (avoid direct exposure to sunlight or artificial ultraviolet light); renal impairment; visual disturbances; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- *Antacids*—absorption of demeclocycline is impaired by concomitant administration of preparations containing calcium, magnesium, aluminium, or sodium bicarbonate.

Pharmacodynamic

- *NSAIDs*—increased risk of nephrotoxicity.
- *Penicillins*—bacteriostatic effect of demeclocycline may reduce bactericidal action of penicillins.
- *Warfarin*—plasma prothrombin activity may be depressed, needing lower warfarin doses.

Dose

Demeclocycline capsules should be swallowed whole with plenty of fluid while sitting or standing. Doses should be taken an hour before, or 2 hours after, meals as absorption is impaired by milk and food.

- Initial dose 900mg to 1200mg daily in 3–4 divided doses.
- If poorly tolerated, a lower initial dose may be used (e.g. 150mg BD to TDS), but time to effect may be delayed.
- Usual maintenance dose is 600mg to 900mg daily in 3–4 divided doses.

Dose adjustments

Elderly

- No specific guidance is available. Use the lowest effective dose.

Hepatic/renal impairment

- No specific guidance is available, although the manufacturer recommends that patients with liver disease should not receive >1g daily and lower doses are indicated in cases of renal impairment to avoid excessive systemic accumulation.
- In both cases, regular blood tests (LFTs, U&Es) are advisable with prolonged therapy.

Additional information

- Demeclocycline can address hyponatraemia in specific patients with SIADH, although efficacy is variable and may depend upon the underlying aetiology. The effect in SIADH should be apparent within 3–5 days.
- The capsule should not be opened for oral administration due to the risk of developing oesophagitis or oesophageal ulceration.
- Treatment of chronic hyponatraemia may require use of prolonged treatment with demeclocycline, potentially at high doses. This may increase the risk of nephrotoxicity and photosensitive skin reactions.

Pharmacology

Demeclocycline is a tetracycline antibiotic. The use in SIADH actually relies on the adverse effect of nephrogenic diabetes insipidus through inhibition of ADH on renal tubules. It undergoes minor hepatic metabolism; the majority of a dose is excreted renally as unchanged drug.

Denosumab ⚠

Prolia® (POM)
Injection (prefilled syringe): 60mg/mL (1).

XGEVA® (POM)
Injection (prefilled syringe): 120mg/1.7mL (1).

Indications

- Prevention of skeletal-related events in adults with advanced malignancies involving bone (*XGEVA®*).
- Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (*XGEVA®*).
- †Treatment of hypercalcaemia of malignancy[1] in the following situations:
  - hypercalcaemia refractory to bisphosphonates
  - intolerance to, or contraindications for, the use of bisphosphonates (e.g. severe renal impairment).
- Indications *not discussed* include:
  - treatment of osteoporosis in post-menopausal women and men at increased risk of fractures (*Prolia®*)
  - treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures (*Prolia®*).

Contraindications and cautions

- Contraindicated for use in patients with:
  - severe untreated hypocalcaemia
  - untreated lesions from dental or oral surgery.
- If present, hypocalcaemia must be corrected prior to treatment with denosumab (unless for treatment of hypercalcaemia of malignancy).
- Patients with severe renal impairment (CrCl <30mL/min) are at greater risk of developing hypocalcaemia.
- Osteonecrosis of the jaw has been reported commonly in patients receiving denosumab. Cancer patients are more likely to be at risk of osteonecrosis as a result of their disease, cancer therapies, and blood dyscrasias. Dental examination and appropriate preventative dentistry are recommended prior to treatment. Dental surgery should be avoided during this treatment. Patients should maintain good oral hygiene while receiving long-term denosumab, receive routine dental check-ups, and be encouraged to report any oral symptoms.
- Atypical femoral fractures have been rarely reported in patients receiving long-term treatment (defined as >2.5 years). Patients should be advised to report any new thigh, hip, or groin pain.
- Osteonecrosis of the external auditory canal has been rarely reported. Patients should be advised to report any ear pain, ear infection, or discharge from the ear.
- A pooled analysis of four phase III studies has shown an increased rate of new primary malignancies in patients given denosumab (1-year cumulative incidence of 1.1%), compared with those given zoledronic

acid (0.6%), when used in the indication of *prevention of skeletal-related events* with advanced malignancies involving bone.[2]
- Three cases of clinically significant hypercalcaemia complicated by acute renal injury have been reported in a clinical trial of adults and skeletally mature adolescents with *giant cell tumour of bone* up to 7 months after treatment cessation.[3] After treatment is discontinued, monitor patients for signs and symptoms of hypercalcaemia, consider periodic assessment of serum Ca^{2+}, and re-evaluate the patient's calcium and vitamin D supplementation requirements.

Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: diarrhoea; dyspnoea; hypocalcaemia (*if severe, complications can include QT prolongation*); musculoskeletal pain (which may be severe).
- *Common*: abdominal discomfort; constipation; hyperhidrosis; hypophosphataemia; infection (upper respiratory tract infection, urinary tract infection); new primary malignancy (see ➔ *Contraindications and cautions*, p. 200); osteonecrosis of the jaw; rash; tooth extraction.
- *Uncommon*: hypercalcaemia (see ➔ *Contraindications and cautions*, p. 200).
- *Rare*: anaphylaxis; atypical femoral fracture; hypersensitivity.
- *Not known*: osteonecrosis of the external auditory canal.

Drug interactions

Pharmacokinetic
- None known.

Pharmacodynamic
- *Aminoglycosides*—may have additive hypocalcaemic effect.

Dose

Prevention of skeletal-related events
- 120mg SUBCUT every 4 weeks.
- Ensure co-prescription of at least calcium 500mg and vitamin D 400 units PO OD, unless hypercalcaemia is present.

Giant cell tumour of bone
- 120mg SUBCUT every 4 weeks, with additional 120mg SUBCUT on days 8 and 15 of the first month.
- Ensure co-prescription of at least calcium 500mg and vitamin D 400 units PO OD, unless hypercalcaemia is present.

[+]Treatment of hypercalcaemia of malignancy
- Consult a specialist for advice (e.g. clinical biochemistry).
- Licensed in the United States for this indication: 120mg SUBCUT every 4 weeks, with additional 120mg SUBCUT on days 8 and 15 of the first month. Usually reserved for refractory hypercalcaemia; the EMA rejected the application in 2016.

- The optimal dose in patients with impaired renal function is unclear, especially as doses as low as 60mg have been associated with hypocalcaemia in these patients.
- Ensure that patients have a 25-hydroxyvitamin D level in excess of 30ng/mL prior to administration of denosumab due to the risk of hypocalcaemia. This is especially important for patients with renal impairment.
- A suggested approach is an initial dose of 0.3mg/kg SUBCUT, with subsequent doses based upon response (recheck serum Ca^{2+} within 5–7 days).[4]
- The median time of response is 9–10 days, based on a dose of 120mg.

Dose adjustments

Elderly

- No dose adjustment is required in elderly patients.

Hepatic/renal impairment

- Denosumab has not been studied in patients with hepatic impairment. It is, however, unlikely to be eliminated via hepatic metabolic mechanisms.
- Dose adjustments are unnecessary for patients with renal impairment. Nonetheless, use with caution in patients with CrCl <30mL/min, due to the increased risk of hypocalcaemia.

Additional information

- Administer SUBCUT in the upper arm, upper thigh, or abdomen.
- *Prolia®* and *XGEVA®* must be stored in a refrigerator. Once removed, they can be stored at room temperature (<25°C) for up to 30 days.
- To avoid discomfort at the site of injection, the vial should be brought to room temperature (up to 25°C) before injecting; inject slowly.

Pharmacology

Denosumab is a human monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL is essential for the formation, function, and survival of osteoclasts, the cells that are responsible for bone resorption, and hence Ca^{2+} release from bone. Parathyroid hormone-related peptide secreted by tumour cells stimulates the formation of RANKL. By binding to RANKL, denosumab reduces osteoclast numbers and activity, reducing bone resorption and cancer-induced bone destruction.

References

1. Thosani S, Hu MI. Denosumab: a new agent in the management of hypercalcemia of malignancy. *Future Oncol*. 2015;**11**(21):2865–71.
2. Medicines and Healthcare products Regulatory Agency. Denosumab (Xgeva▼) for advanced malignancies involving bone: study data show new primary malignancies reported more frequently compared to zoledronate. 2018. Available from: https://www.gov.uk/drug-safety-update/denosumab-xgeva-for-advanced-malignancies-involving-bone-study-data-show-new-primary-malignancies-reported-more-frequently-compared-to-zoledronate. Accessed 12 July 2018.
3. Uday S, Gaston CL, Rogers L, *et al*. Osteonecrosis of the jaw and rebound hypercalcemia in young people treated with denosumab for giant cell tumor of bone. *J Clin Endocrinol Metab*. 2018;**103**(2):596–603.
4. Cicci JD, Buie L, Bates J, van Deventer H. Denosumab for the management of hypercalcemia of malignancy in patients with multiple myeloma and renal dysfunction. *Clin Lymphoma Myeloma Leuk*. 2014;**14**(6):e207–11.

Dexamethasone

Tablets are formulated as dexamethasone base; soluble tablets, oral solution, and injection are formulated as dexamethasone sodium phosphate. All formulation strengths and doses are quoted as dexamethasone base. To avoid administration issues, healthcare professionals are encouraged to prescribe doses in terms of dexamethasone base. The oral bioavailability of dexamethasone (base) is variable; there are two injection formulations, so for ease of administration, 4mg PO ≈ 3.3mg to 3.8mg given parenterally.

Generic (POM)

Tablet: 0.5mg (28; 30); 2mg (50; 100; 500); 4mg (50); 40mg (10).
Soluble tablet: 2mg (50); 4mg (50); 8mg (50).
Oral solution (sugar-free): 2mg/5mL (150mL); 10mg/5mL (50mL; 150mL); 20mg/5mL (50mL).
Injection: 3.3mg/mL (5; 10); 3.8mg/mL (10); 6.6mg/2mL (5; 10) (all strengths quoted as dexamethasone base).

Indications

- Suppression of inflammation (including cerebral oedema).
- Immunosuppression (see ➔ *Additional information*, p. 208).
- [+]Appetite stimulation.
- [+]Bowel obstruction.
- [+]Dyspnoea.
- [+]Hypercalcaemia (associated with granulomatous causes, e.g. lymphoma, sarcoidosis).
- [+]Nausea and vomiting.
- [+]Pain (e.g. bone pain, nerve compression).
- [+]Spinal cord compression.
- [+]Superior vena cava obstruction.

Contraindications and cautions

- In general, contraindications are relative in conditions where the use of dexamethasone may be lifesaving.
- Use of dexamethasone is contraindicated in systemic infection unless specific anti-infective therapy is employed.
- Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster.
- The MHRA has warned that corticosteroids carry a rare risk of central serous chorioretinopathy with both local and systemic therapy. Patients should be advised to report any blurred vision or visual disturbances.
- Dexamethasone may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Caution is advised when considering the use of systemic corticosteroids in patients with the following conditions:
  - concurrent use of NSAIDs (see ➔ *Drug interactions*, p. 205)
  - congestive heart failure
  - diabetes mellitus (risk of hyperglycaemia—close monitoring of blood glucose recommended)
  - epilepsy (see ➔ *Drug interactions*, p. 205)

- glaucoma
- hypertension
- hypokalaemia (correct before starting dexamethasone)
- hepatic impairment (see ➔ *Dose adjustments*, p. 207)
- osteoporosis; recent myocardial infarction (risk of myocardial rupture)
- renal impairment (see ➔ *Dose adjustments*, p. 207)
- peptic ulceration
- psychotic illness (symptoms can emerge within a few days or weeks of starting the treatment).

- In the presence of significant illness, trauma, or surgery, patients who have taken dexamethasone at doses >1mg PO OD, or stopped treatment within the past 3 months, may need additional corticosteroid treatment to compensate for a reduced adrenocortical response (e.g. IV hydrocortisone).

Dexamethasone withdrawal

In patients who have received more than physiological doses of systemic corticosteroids (i.e. >1mg dexamethasone) for >3 weeks, withdrawal should be gradual to avoid acute adrenal insufficiency. The speed of withdrawal should be determined on an individual basis. Abrupt withdrawal is unlikely to lead to clinically relevant hypothalamic–pituitary–adrenal axis suppression.

Consider gradual withdrawal for patients with the following:

- doses of systemic corticosteroid >4mg to 6mg PO OD of dexamethasone for >1 week
- received regular night-time doses
- received >3 weeks' treatment
- repeated courses of systemic steroids (especially if >3 weeks)
- short course within 1 year of stopping long-term treatment
- other causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in patients whose disease is unlikely to relapse *and* who have received treatment for ≤3 weeks *and* are not included in the groups above.

There is no evidence as to the best way to withdraw corticosteroids and it is often performed with close monitoring of the patient's condition. The dose may initially be reduced rapidly (e.g. by halving the dose daily) to physiological doses (approximately 1mg dexamethasone) and then more slowly (e.g. 500 micrograms/week for 1–2 weeks).

A 'withdrawal syndrome' may also occur, including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful and itchy skin nodules, and loss of weight.

In patients approaching the end of life, once the decision is made to withdraw corticosteroids, these can be discontinued abruptly. Patients with brain tumours may require additional analgesia, as raised intracranial pressure can develop and may manifest as worsening headache or terminal restlessness. If necessary, treatment can be continued via the SUBCUT route.

Adverse effects

The frequency is not defined. Adverse effects are generally predictable and related to dosage, timing of administration, and duration of treatment. Refer to the SmPC for a full list of adverse effects. They include:

- endocrine:
  - hirsutism; hyperglycaemia; hyperlipidaemia; weight gain
- fluid and electrolyte disturbances:
  - congestive heart failure; hypertension; hypokalaemia; Na^+ and water retention
- GI:
  - acute pancreatitis; dyspepsia; peptic ulceration with perforation; haemorrhage; hiccups (if problematic, may resolve if alternative corticosteroid used)
- musculoskeletal:
  - aseptic necrosis of the femoral head; avascular necrosis; loss of muscle mass; osteoporosis; myopathy (can present within 2 weeks of high-dose treatment); tendon rupture
- neurological:
  - aggravation of epilepsy; anxiety; confusion; depression; insomnia; mood elevation; psychotic reactions (management of corticosteroid-induced psychiatric reactions involves dose reduction or discontinuation)
- other:
  - glaucoma; impaired wound healing; increased susceptibility and severity of infections (signs can be masked); multiple myeloma patients treated with lenalidomide or thalidomide, in combination with dexamethasone, may have an increased risk of thromboembolic events; sweating.

Corticosteroid-induced osteoporosis

- Patients aged over 65 years and with prior or current exposure to oral corticosteroids are at increased risk of osteoporosis and bone fracture. Treatment with corticosteroids for periods as short as 3 months may result in increased risk. Three or more courses of corticosteroids taken in the previous 12 months are considered to be equivalent to at least 3 months of continuous treatment.
- Prophylactic treatment (e.g. bisphosphonate, calcium and vitamin D supplements, hormone replacement therapy) should be considered for all patients who may take an oral corticosteroid for 3 months or longer.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Dexamethasone is a substrate of CYP3A4/5. It is also a moderate inducer of CYP3A4/5 at doses ≥16mg/day. Co-administration with drugs that are metabolized by, or affect the activity (induction or

inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Note that low activity of CYP3A4 (e.g. through inhibition) can contribute to the development of dexamethasone-induced osteonecrosis of the femoral head.
- *Carbamazepine*—effect of dexamethasone likely to be reduced; consider doubling the dexamethasone dose and monitor the response.
- *Colestyramine*—may decrease absorption of dexamethasone.
- *Clarithromycin/erythromycin*—may increase the effects of dexamethasone through inhibition of CYP3A4.
- *Phenytoin*—effect of dexamethasone likely to be reduced—consider doubling the dexamethasone dose and monitor the response; phenytoin plasma concentrations may also be affected (increased or decreased).
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of dexamethasone through inhibition of intestinal CYP3A4.

Pharmacodynamic
- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—effect antagonized by dexamethasone.
- *Azathioprine*—additive immunosuppressive effect.
- *Ciclosporin*—additive immunosuppressive effect; convulsions reported with combination.
- *Diuretics*—effect antagonized by dexamethasone; increased risk of hypokalaemia and hyperglycaemia.
- *Hypoglycaemic drugs*—effect antagonized by dexamethasone.
- *NSAIDs*—increased risk of GI toxicity.
- *SSRIs*—increased risk of bleeding.
- *Thalidomide*—toxic epidermal necrolysis reported with concurrent use.

Dose

Cerebral oedema
- Initial dose (mild symptoms) 4mg to 8mg PO OM; initial dose (moderate to severe symptoms) 8mg to 16mg PO OM (or 4mg to 8mg PO BD, last dose 2 p.m.).
- Alternatively, by SUBCUT injection:
  - 1.65mg to 6.6mg BD (0.5mL to 2mL of *3.3mg/mL*); last dose 2 p.m., or
  - 1.9mg to 7.6mg BD (0.5mL to 2mL of *3.8mg/mL*); last dose 2 p.m.
- †Alternatively, via CSCI over 24 hours:
  - 3.3mg to 13.2mg (1mL to 4mL of *3.3mg/mL*), or
  - 3.8mg to 15.2mg (1mL to 4mL of *3.8mg/mL*)
- Review after 2–4 days and consider stopping over 5–7 days.

†Appetite
- Initial dose 2mg to 6mg PO OM. Dose reduction should be guided by symptom response.

†Bowel obstruction/†spinal cord compression/†superior vena cava obstruction
- Initial dose 8mg to 16mg PO OM (or 4mg to 8mg PO BD, last dose 2 p.m.).

- Alternatively, by SUBCUT injection:
  - 3.3mg to 6.6mg BD (1mL to 2mL of *3.3mg/mL*); last dose 2 p.m., or
  - 3.8mg to 7.6mg BD (1mL to 2mL of *3.8mg/mL*); last dose 2 p.m.
- Alternatively, via CSCI over 24 hours:
  - 6.6mg to 13.2mg (2mL to 4mL of *3.3mg/mL*), or
  - 7.6mg to 15.2mg (2mL to 4mL of *3.8mg/mL*)
- Review after 2–4 days. Dose reduction should be guided by symptom response.

+Dyspnoea/+pain
- Initial dose 4mg to 8mg PO OM (or 2mg to 4mg PO BD, last dose 2 p.m.).
- Alternatively, by SUBCUT injection:
  - 1.65mg to 3.3mg BD (0.5mL to 1mL of *3.3mg/mL*); last dose 2 p.m., or
  - 1.9mg to 3.8mg BD (0.5mL to 1mL of *3.8mg/mL*); last dose 2 p.m.
- Alternatively, via CSCI over 24 hours:
  - 3.3mg to 6.6mg (1mL to 2mL of *3.3mg/mL*), or
  - 3.8mg to 7.6mg (1mL to 2mL of *3.8mg/mL*)
- Dose adjustment should be guided by symptom response.

+Hypercalcaemia
- Initial dose 4mg to 8mg PO OM (or 2mg to 4mg PO BD, last dose 2 p.m.) for up to 5 days.
- Alternatively, by SUBCUT injection for up to 5 days:
  - 1.65mg to 3.3mg BD (0.5mL to 1mL of *3.3mg/mL*); last dose 2 p.m., or
  - 1.9mg to 3.8mg BD (0.5mL to 1mL of *3.8mg/mL*); last dose 2 p.m.
- Alternatively, via CSCI over 24 hours for 5 days:
  - 3.3mg to 6.6mg (1mL to 2mL of *3.3mg/mL*), or
  - 3.8mg to 7.6mg (1mL to 2mL of *3.8mg/mL*).
- Subsequent doses should be guided by biochemistry, but long-term treatment (e.g. 2mg PO OD) may be required.

+Nausea and vomiting
- Initial dose 4mg to 16mg PO OM (or 2mg to 8mg PO BD, last dose 2 p.m.)
- Alternatively, by SUBCUT injection:
  - 1.65mg to 6.6mg BD (0.5mL to 2mL of *3.3mg/mL*); last dose 2 p.m., or
  - 1.9mg to 7.6mg BD (0.5mL to 2mL of *3.8mg/mL*); last dose 2 p.m.
- Alternatively, via CSCI over 24 hours:
  - 3.3mg to 13.2mg (1mL to 4mL of *3.3mg/mL*), or
  - 3.8mg to 15.2mg (1mL to 4mL of *3.8mg/mL*).
- Dose adjustment should be guided by symptom response.

Dose adjustments

Elderly
- No specific dose adjustments are necessary. Use the lowest dose for the shortest duration possible since the elderly are more susceptible to adverse effects.

Hepatic/renal impairment

- The SmPC states that empirical dose adjustments may be necessary in patients with severe hepatic impairment, due to reduced metabolism and hypoalbuminaemia.
- In patients undergoing active haemodialysis, the SmPC states that there may be increased clearance of dexamethasone via the dialysate and therefore, dose adjustments may be required.
- In all cases, the lowest effective dose should be used for the shortest duration possible.

Additional information

- The immunosuppressant activity of dexamethasone can be used at the end of life to manage the symptoms associated with transplant rejection (e.g. pain and rejection of a kidney). Seek specialist advice.
- Consider oral hygiene with dexamethasone use. The patient may develop oral candidosis and may need a course of nystatin (or fluconazole).
- Oral anti-inflammatory corticosteroid equivalences are:
  - dexamethasone 750 micrograms = hydrocortisone 20mg = prednisolone 5mg.
- Low-dose (0.5mg to 1mg) dexamethasone is occasionally added to CSCIs in some centres to reduce site reactions. Unless specific compatibility is available, this practice cannot be recommended.
- Dexamethasone is *chemically and physically* compatible under stated conditions with furosemide, granisetron, hydromorphone, ketamine, ondansetron, oxycodone, and tramadol. Under stated conditions, dexamethasone is *physically* compatible with alfentanil, Buscopan®, clonazepam, cyclizine, diamorphine, dihydrocodeine, fentanyl, haloperidol (low-dose dexamethasone), hyoscine hydrobromide, methadone, metoclopramide, morphine hydrochloride, morphine sulfate, morphine tartrate, and parecoxib.[1]
- Dexamethasone should be administered alone via CSCI, unless specific compatibility data are available.
- Combination with midazolam should be avoided.[1]
- Betamethasone (as sodium phosphate) via SUBCUT injection or CSCI has anecdotally been used successfully as a substitute in situations of dexamethasone unavailability (4mg/mL betamethasone ≈ 3.3/3.8mg/mL dexamethasone).

Pharmacology

Dexamethasone is a highly potent and long-acting glucocorticoid with negligible mineralocorticoid effects. Like other glucocorticoids, dexamethasone also has anti-allergic, antipyretic, and immunosuppressive properties. It is metabolized mainly in the liver, with some occurring in the kidney. Dexamethasone and its metabolites are excreted in the urine.

Reference

1. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Diamorphine

Generic (CD2 POM)
Injection: 5mg (5); 10mg (5); 30mg (5); 100mg (5); 500mg (5).

Indications

- Relief of severe pain.
- †Painful skin lesions (topical).[1]
- †Mucositis (topical).[1]
- †Dyspnoea.[2]

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care, although there may be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation). Nonetheless, the SmPC states that diamorphine is contraindicated for use in patients with:
  - biliary colic
  - obstructive airways disease (may release histamine)
  - phaeochromocytoma (due to the risk of pressor response to histamine release)
  - respiratory depression.
- Avoid concurrent administration of MAOIs or within 2 weeks of discontinuation of their use (NB—initial low doses of *morphine*, careful titration, and close monitoring may permit safe combination).
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29), when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 210). Of the opioids, *morphine* is believed to carry the lowest risk. Nonetheless, treatment must be reviewed urgently if symptoms develop, diamorphine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[3] The SmPC warns that concurrent use of diamorphine and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- If appropriate, consideration should be given to use of diamorphine in the following instances:
  - acute alcoholism
  - Addison's disease (adrenocortical insufficiency)
  - asthma (may release histamine)

  - constipation
  - delirium tremens
  - diarrhoea (may mask underlying severe constipation)
  - diseases of the biliary tract
  - elderly patients
  - head injury
  - hepatic impairment (see ➔ *Dose adjustments*, p. 212)
  - history of alcohol and drug abuse
  - hypotension associated with hypovolaemia (diamorphine may result in severe hypotension)
  - hypothyroidism
  - inflammatory bowel disorders
  - pancreatitis
  - prostatic hypertrophy
  - raised intracranial pressure
  - renal impairment (see ➔ *Dose adjustments*, p. 212)
  - sleep apnoea (respiratory effects of opioids are more pronounced during sleep).
- Diamorphine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

☹ Adverse effects

Strong opioids tend to cause similar adverse effects, albeit to varying degrees. The frequency is not defined, but reported adverse effects include the following. Refer to the SmPC for a full list of adverse effects.

- anorexia; biliary pain; confusion; constipation; drowsiness; dry mouth; dyspepsia; euphoria; insomnia; headache; hyperhidrosis; myoclonus; nausea; pancreatitis exacerbation; pruritus; sexual dysfunction (e.g. amenorrhoea, decreased libido, erectile dysfunction); urinary retention; vertigo; visual disturbance; vomiting; weakness.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- No clinically significant pharmacokinetic interactions reported.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 209.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing affect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of morphine may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOI*—risk of severe and unpredictable interactions with MAOIs, involving the potentiation of opioid or serotonergic effects.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 209.

Dose

Note that it is generally accepted that PRN doses may be given every 2–4 hours (some centres suggest a maximum daily limit of six doses, irrespective of indication). In the case of severe pain or end-of-life care (e.g. pain, dyspnoea, cough), PRN doses may be given as frequently as every hour under specialist supervision.

Relief of severe pain

- The initial dose of diamorphine depends upon the patient's previous opioid requirements. Refer to ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences. Refer to ➔ Chapter 2, *Breakthrough cancer pain*, p. 54 for guidance relating to BTcP.
- Initial dose in opioid-naïve patients is 2.5mg SUBCUT every 4–6 hours PRN (or more frequently, as described above).
- Alternatively, 10mg via CSCI over 24 hours and increase as necessary.
- Diamorphine is very soluble in water; 1g dissolves in 1.6mL of water, permitting high doses via SUBCUT injections.

[+]Painful skin lesions (topical)

- As with morphine, often use 0.1% or 0.125% w/w gels initially. These can be prepared immediately prior to administration by adding 10mg diamorphine injection (diluted with 0.5mL WFI) to 8g Intrasite® gel (making a 0.125% w/w gel). Higher-strength gels, typically up to 0.5%, can be made if necessary.
- Initial dose: using 0.125% gel (10mg diamorphine in 8g Intrasite® gel), apply 5–10mL to the affected area at dressing changes (up to TDS). Rinse the wound with NaCl before reapplying the next dose.
- Use within 1 hour of preparation and discard any remaining product.

+Mucositis

- As with morphine, often use 0.1% w/v initially. Preparations should be prepared immediately prior to administration by adding 10mg diamorphine injection (diluted with 0.5mL WFI) to 10mL of a suitable carrier (e.g. Gelclair®, Oral Balance Gel®).
- For higher-strength preparations, up to 0.5% w/v can be used if required.
- Initial dose: 10mg to the affected area BD to TDS.
- Use within 1 hour of preparation and discard any remaining product.

+Dyspnoea

- For opioid-naïve patients, initial dose is 1.25mg SUBCUT every 4–6 hours PRN (or more frequently, as described above). If patients require >2 doses daily, use of a CSCI should be considered.
- In patients established on opioids, a dose that is equivalent to 25% of the current PRN rescue analgesic dose may be effective. This can be increased up to 100% of the rescue dose in a graduated fashion.

Dose adjustments

Elderly

- No specific guidance is available, although lower starting doses in opioid naïve patients may be preferable. Dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance is available, although in patients with hepatic impairment, the plasma concentration is expected to be increased. In view of its eventual hepatic metabolism, caution is advised when giving diamorphine to patients with hepatic impairment. Lower starting doses in opioid-naïve patients may be preferable and dose requirements should be individually titrated.
- No specific guidance is available for patients with renal impairment. However, in view of the fact that the active metabolite morphine-6-glucuronide is renally excreted, lower starting doses in opioid-naïve patients may be preferable and dose requirements should be individually titrated. Alternatively, a different opioid may be more appropriate (e.g. *alfentanil*, *hydromorphone*, *oxycodone*, *fentanyl*).

Additional information

- The UK is one of the few places where diamorphine is used medicinally, although it has become less popular as morphine sulfate is suitable in most cases. Its use developed in palliative care mainly because high solubility in water enables large doses to be included in the contents of a CSCI.
- If other analgesic measures are introduced—pharmacological or other alternatives, e.g. radiotherapy—the dose of diamorphine may need to be reduced.
- Diamorphine displays concentration-dependent incompatibility with cyclizine. Mixtures are chemically and physically stable in WFI up to concentrations of 20mg/mL over 24 hours. If the diamorphine

concentration exceeds 20mg/mL, crystallization may occur unless the concentration of cyclizine is no greater than 10mg/mL. Similarly, if the concentration of cyclizine exceeds 20mg/mL, crystallization may occur unless the concentration of diamorphine is no greater than 15mg/mL.
- The pH of the combination must remain below 6 for diamorphine to remain in solution.
- Diamorphine is *chemically and physically* compatible under stated conditions with Buscopan®, cyclizine, haloperidol, hyoscine hydrobromide, ketorolac, metoclopramide, and midazolam. Under stated conditions, diamorphine is *physically* compatible with dexamethasone, furosemide, levomepromazine, octreotide, and ondansetron.[4]

Pharmacology

Diamorphine is a synthetic opioid agonist, with about one-and-a-half times the potency of morphine when both are given parenterally. Given orally, both diamorphine and morphine are considered equianalgesic. It interacts predominantly with the MOR. Diamorphine is rapidly deacetylated to the active metabolite 6-mono-acetylmorphine (6-MAM), which is also rapidly deacetylated to morphine. Metabolism is then as for morphine.

References

1. Leppert W, Malec-Milewska M, Zajaczkowska R, Wordliczek J. Transdermal and topical drug administration in the treatment of pain. *Molecules*. 2018;**23**(3):681.
2. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev*. 2016;**3**:CD011008.
3. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
4. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Diazepam

Generic (CD4a)
Tablet: 2mg (28); 5mg (28); 10mg (28).
Oral suspension: 2mg/5mL (100mL).
Oral solution: 2mg/5mL (100mL).
Injection (emulsion): 10mg/2mL (10).
Injection (solution): 10mg/2mL (10).
Rectal solution: 2.5mg/1.25mL (5); 5mg/2.5mL (5); 10mg/2.5mL (5).

Indications

Indications vary—refer to the individual SmPC. They include:
- anxiety (short-term use only)
- †dyspnoea (associated with anxiety)
- insomnia (short-term use only)
- muscle spasm
- status epilepticus.

Contraindications and cautions

- Is contraindicated for use in patients with:
  - acute porphyria
  - acute pulmonary insufficiency
  - myasthenia gravis (may exacerbate condition)
  - severe hepatic insufficiency
  - sleep apnoea syndrome.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of diazepam and opioids increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Suicidal ideation and behaviour have been reported with anti-epileptics.
- Diazepam should not be used alone in the treatment of depression or anxiety associated with depression, due to the risk of precipitation of suicide.
- Use with caution if there is a history of drug or alcohol abuse.
- Diazepam should be used with caution in patients with chronic respiratory disease, renal impairment, or moderate hepatic impairment.
- Dose reductions may be necessary in the elderly (see *Dose adjustments*, p. 216).
- Avoid abrupt withdrawal, even if short duration treatment. Prolonged use of benzodiazepines may result in the development of dependence, with subsequent withdrawal symptoms on cessation of use, e.g. agitation, anxiety, confusion, headaches, irritability, panic, restlessness, sleep disturbances, sweating, and tremor. The risk of dependence

increases with dose and duration of treatment. Gradual withdrawal is advised.
- Diazepam may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: drowsiness.
- *Common*: ataxia; confusion; fatigue; tremor; withdrawal symptoms.
- *Uncommon*: allergic skin reactions; anterograde amnesia (reduce risk by ensuring 7–8 hours of *uninterrupted* sleep); constipation; diarrhoea; dizziness; headache; myasthenia; nausea; respiratory depression; slurred speech; vomiting.
- *Rare*: blood dyscrasias; depression; dry mouth; gynaecomastia; impotence; incontinence; jaundice; LFT anomalies; paradoxical reactions (aggression, agitation, delusion, excitation, hallucinations, nightmares); urinary retention.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Diazepam is a major substrate of CYP2C19 and CYP3A4/5. Unexplained effects may be explained by the fact that up to 5% of the Caucasian population are CYP2C19 poor metabolizers. The final pathway of diazepam metabolism involves glucuronidation of an active metabolite (oxazepam) via UGT1A9, UGT2B15, and UGT2B7. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Antacids*—may delay the absorption of diazepam.
- *Carbamazepine*—may reduce the effect of diazepam.
- *Clarithromycin*—plasma concentration of diazepam *may* be increased through inhibition of CYP3A4.
- *Corticosteroids*—may reduce the effect of diazepam (e.g. high-dose dexamethasone).
- *Erythromycin*—plasma concentration of diazepam *may* be increased through inhibition of CYP3A4.
- *Esomeprazole*—plasma concentration of diazepam *may* be increased through inhibition of CYP2C19.
- *Fluconazole*—plasma concentration of diazepam *may* be increased through inhibition of CYP2C19.
- *Modafinil*—may increase the effect of diazepam.
- *Omeprazole*—plasma concentration of diazepam *may* be increased through inhibition of CYP2C19.

- *Phenytoin*—can reduce the effect of diazepam.
- *Sodium valproate*—may increase the effect of diazepam (protein-binding displacement; UGT2B15 inhibition).
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of diazepam through inhibition of intestinal CYP3A4.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Alcohol*—may precipitate seizures.
- *Antidepressants*—reduced seizure threshold.
- *Antipsychotics*—reduced seizure threshold.
- *Baclofen*—increased risk of sedation.
- *CNS depressants*—additive sedative effect.
- *Opioids*—see *Contraindications and cautions*, p. 214.

Dose

Anxiety

- Patients may require lower than licensed doses. Initial dose 2mg PO at bedtime, increasing gradually, as required, to 2mg PO TDS. The dose can then be increased, as necessary, to a maximum of 30mg PO daily in divided doses.

Insomnia

- Other drugs are preferable (e.g. zolpidem).
- Patients may require lower than licensed doses. Initial dose 2mg PO at bedtime, increasing gradually, as necessary, to 15mg PO at bedtime.
- Note that patients with insomnia related to anxiety may benefit from a single dose at bedtime (e.g. 10mg to 15mg PO ON).

Status epilepticus

- Other treatment options may be preferable (e.g. buccal/intranasal midazolam).
- 10mg to 20mg PR, repeated after 10–15 minutes if necessary (rectal solution).
- 10mg IV at a rate of 1mL (5mg)/min, repeated if necessary after 10 minutes (injection).

Muscle spasm

- Patients may require lower than licensed doses. Initial dose 2mg PO at bedtime, increasing gradually, as required, to 2mg PO TDS. The dose can then be increased, as necessary, to a maximum of 60mg PO daily in divided doses.

Dose adjustments

Elderly

- Generally, adopt half the normal adult dose.

Hepatic/renal impairment

- No specific guidance available. Patients with hepatic or renal impairment may be particularly susceptible to adverse effects and lower initial doses should be used.

Additional information

- Diazepam has a long duration of action due to several active metabolites. The formation of these is highly variable and treatment must therefore be individualized. Some patients may be able to take diazepam OD due to the presence of an active metabolite with a long half-life.
- If there are unexpected responses, such as excessive sedation, consider drug interactions which could be additive.

Pharmacology

The exact mechanism of action is unknown, but it is believed to act as a modulator of the $GABA_A$ receptor, thereby enhancing GABA-ergic transmission in the CNS. Diazepam undergoes first-pass metabolism via cytochromes CYP2C19 and CYP3A4. Numerous active metabolites are formed, including desmethyldiazepam (major) and temazepam (minor). The main metabolite is desmethyldiazepam, which has a half-life of between 30 and 150 hours. It is further metabolized by glucuronidation (to form nordiazepam O-glucuronide) and by CYP3A4/5 (to form oxazepam). Temazepam is metabolized primarily by glucuronidation via UGT2B7 to the O-conjugate of temazepam, while <5% is metabolized via CYP2C19 and CYP3A4 to oxazepam. Inactivation of oxazepam is by glucuronidation, mediated by UGT1A9 and UGT2B15. CYP2C19 and UGT2B15 are subject to genetic polymorphism; the clinical significance for diazepam use is unclear.

Reference

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.

Diclofenac

Diclofenac sodium

Standard-release
Voltarol® (POM)
Injection: 75mg/3mL (10).
Suppository: 12.5mg (10); 25mg (10); 50mg (10); 100mg (10).

Generic (POM)
Tablet (enteric-coated): 25mg (84); 50mg (28; 84; 100).
Suppository: 100mg (10).

Modified-release
Generic (POM)
Tablet: 75mg (28; 56); 100mg (28) (various branded generics available).
Capsule: 75mg (56); 100mg (28).

Arthrotec® 50 (POM)
Tablet: diclofenac sodium 50mg, misoprostol 200 micrograms (60).

Arthrotec® 75 (POM)
Tablet: diclofenac sodium 75mg, misoprostol 200 micrograms (60).

Generic (POM)
Tablet: diclofenac sodium 50mg, misoprostol 200 micrograms (60).
Tablet: diclofenac sodium 75mg, misoprostol 200 micrograms (60).

Diclofenac potassium

Voltarol® Rapid (POM)
Tablet: 50mg (30).

Generic (POM)
Tablet: 25mg (28); 50mg (28).

Indications

- Relief of pain and inflammation in several conditions:
  - acute gout
  - migraine
  - musculoskeletal disorders
  - pain resulting from trauma
  - rheumatoid arthritis
  - †pain associated with cancer.[1,2]

Contraindications and cautions

- Contraindicated for use in patients with:
  - a history of peptic ulceration related to previous NSAID treatment
  - active, or a history of, recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
  - cerebrovascular disease
  - congestive heart failure (NYHA classes II–IV)

  - severe hepatic impairment; hypersensitivity reactions to ibuprofen, aspirin, or other NSAIDs (e.g. asthma, nasal polyps, rhinitis)
  - ischaemic heart disease; peripheral arterial disease
  - acute porphyria
  - proctitis (suppositories)
  - severe renal impairment.
- Use the minimum effective dose for the shortest duration necessary in order to reduce the risk of CV and GI events. Treatment should be reviewed after *2 weeks*. In the absence of benefit, other options should be considered.
- Elderly patients are more at risk of developing adverse effects.
- Use with caution in the following circumstances:
  - asthma (risk of bronchospasm)
  - atopy (risk of angioedema, bronchospasm, or urticaria)
  - concurrent use of diuretics, corticosteroids, and NSAIDs (see ➔ *Drug interactions*, p. 220)
  - congestive heart failure (NYHA class I)
  - Crohn's disease
  - diabetes mellitus (isolated reports of hypoglycaemic and hyperglycaemic effects; also may increase CV risk)
  - mild to moderate hepatic impairment
  - hyperlipidaemia
  - hypertension (particularly uncontrolled)
  - recovery from surgery
  - mild to moderate renal impairment
  - chronic rhinitis (risk of angioedema, bronchospasm, or urticaria)
  - smoking (higher risk of CV and GI toxicity)
  - ulcerative colitis.
- Patients known to be CYP2C9 poor metabolizers should be treated with caution because there is an increased risk of adverse effects; similarly, drugs that inhibit CYP2C9 should be used with caution (see ➔ *Drug interactions*, p. 220). In both cases, the prescriber should consider reducing the dose to half the lowest recommended dose.
- Before initiating longer-term treatment, risk factors for CV disease should be considered (e.g. diabetes mellitus, hyperlipidaemia, hypertension, smoking).
- Patients taking long-term therapy need regular monitoring of renal and liver function.
- Abnormal LFTs can occur, which may be the result of hypersensitivity, rather than direct toxicity. Nonetheless, discontinue NSAID if this persists.
- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of diclofenac. Patients appear to be at highest risk within the first month of treatment. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with diclofenac must not be restarted.
- Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms can include chest pain occurring in association with an allergic reaction to diclofenac.

- Patients with SLE and mixed connective tissue disorders may be at risk of developing aseptic meningitis.
- Diclofenac may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Consider co-prescription of misoprostol or a PPI if at high risk of NSAID-induced GI toxicity, e.g. long-term NSAID therapy, concurrent use of drugs that increase the risk of GI toxicity (see ➔ *Drug interactions*).
- Refer to ➔ Chapter 2, *Selection of an NSAID*, p. 49 for further information about selecting an NSAID.
- Diclofenac may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; anorexia; diarrhoea; dizziness; dyspepsia; elevated LFTs (discontinue if this persists); flatulence; headache; nausea; rashes; vertigo; vomiting.
- *Uncommon*: cardiac failure; chest pain; myocardial infarction; palpitations.
- *Rare*: asthma; drowsiness; gastritis; GI haemorrhage; GI ulcer; haematemesis; hepatitis; hypersensitivity reactions; jaundice; melaena; oedema; urticaria.
- *Very rare*: acute renal failure; agranulocytosis; anaemia (aplastic, haemolytic); anxiety; aseptic meningitis; blurred vision; bullous eruptions; colitis; constipation; eczema; erythema multiforme; haematuria; hepatitis; hypertension; glossitis; leucopenia; oedema; pancreatitis; photosensitivity; pneumonitis; Stevens–Johnson syndrome; stomatitis; thrombocytopenia; tinnitus; toxic epidermal necrolysis; vasculitis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Diclofenac is metabolized primarily by CYP2C9 and UGT2B7. Minor pathways involve CYP2B6, CYP2C8, CYP2C19, and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (see ➔ *Cytochrome P450 tables* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index. Note that co-administration of an enzyme inhibitor is unlikely to be clinically significant due to metabolism via multiple pathways.
- *Antacids*—avoid giving within 1 hour of enteric-coated tablets.
- *Cannabidiol*—inhibits UGT2B7, but clinical significance is unknown.
- *Colestipol/colestyramine*—take diclofenac at least 1 hour or 4–6 hours afterwards.
- *Fluconazole*—plasma concentration of diclofenac may be increased.
- *Lithium*—reduced excretion of lithium.
- *Methotrexate*—reduced excretion of methotrexate.

- *Miconazole*—may increase the effectiveness of diclofenac and risk of adverse effects.
- *Phenytoin*—monitoring of serum phenytoin is recommended.
- *Rifampicin*—can reduce the effectiveness of diclofenac.
- *Warfarin*—possible increased risk of bleeding through competitive inhibition of warfarin metabolism (5–11% of Caucasians have a variant of CYP2C9, requiring lower maintenance doses of warfarin; combination with diclofenac may further reduce warfarin metabolism).

Pharmacodynamic
- *ACE-Is/ARBs*—risk of AKI.
- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—reduced antihypertensive effect.
- *Antiplatelet drugs*—increased risk of bleeding.
- *Corticosteroids*—increased risk of GI toxicity.
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Digoxin*—monitoring of serum digoxin is recommended.
- *Diuretics*—reduced diuretic effect; risk of AKI.
- *Quinolone antibiotics*—risk of convulsions.
- *SSRIs*—increased risk of GI bleeding.
- *Trimethoprim*—increased risk of hyperkalaemia.

Dose

Diclofenac, even in doses available OTC, elevates the risk of CV toxicity. Where possible, other NSAIDs should be considered.

Ensure gastroprotection (e.g. PPI) is prescribed for patients at risk of NSAID-induced GI toxicity.

Standard-release
- Initial dose 50mg PO BD, increasing to 50mg PO TDS, with or after food, as necessary.
- The rectal route is generally avoided in palliative care. Nonetheless, it may be preferable to a CSCI. The usual dose is 75mg to 150mg daily in divided doses.
- †Although other NSAIDs are generally preferred, diclofenac can be given as 100mg to 150mg via CSCI over 24 hours. Note diclofenac should not be mixed with other drugs and a separate CSCI will be needed. Dilute CSCI with NaCl.

Modified-release
- Dose 75mg to 100mg PO OD or 75mg PO BD, with or after food.

Dose adjustments

Elderly
- The elderly are at increased risk of adverse effects. Use the lowest effective dose and for the shortest duration possible.

Hepatic/renal impairment

- Diclofenac is contraindicated for use in patients with severe hepatic or renal impairment.
- In patients with mild to moderate liver impairment, no specific dose recommendations are available and the metabolism of diclofenac is stated to be unaffected. However, the lowest dose possible should be used for the shortest duration possible and the patient should be closely monitored. If abnormal LFTs develop and persist or deteriorate further, diclofenac must be discontinued.
- Use of diclofenac may result in deterioration of renal function. The lowest effective dose should be used, and renal function monitored.

Additional information

- Ensure a PPI or H_2 antagonist is not co-prescribed with diclofenac/misoprostol combinations.
- Diclofenac is currently one of three NSAID drugs that have reportedly been given via a CSCI, the other two being ketorolac and parecoxib. Since diclofenac can cause irritation at the site of infusion, ketorolac or parecoxib may be preferable. Until recently, only *Voltarol*® ampoules were available and all evidence relating to CSCI use relates to this product. *AKIS*® solution for injection has recently been introduced. This product is formulated differently and presently its suitability for administration via CSCI remains uncertain.
- Diclofenac should be administered via separate CSCI (using *Voltarol*® ampoules) because the high pH of the formulation renders it incompatible with the majority of drugs likely to be administered by this route.

Pharmacology

Diclofenac is an NSAID with analgesic, anti-inflammatory, and antipyretic properties. The potassium salt of diclofenac is more rapidly absorbed. The mechanism of action of diclofenac, like that of other NSAIDs, is not completely understood but may be related to inhibition of COX-1 and COX-2. Diclofenac is believed to be more selective for COX-2 and indeed has been shown to have a CV profile that is similar to that of COX-2 inhibitors.

Diclofenac is rapidly and completely absorbed after oral administration, although the bioavailability is slightly less with dispersible tablets. Oral bioavailability is about half that of an equivalent parenteral dose, presumably as a result of high first-pass metabolism. It is highly protein-bound to albumin (about 99%) and extensively metabolized in the liver via a variety of pathways (involving UGT2B7, CYP2C9 (major), CYP2B6, CYP2C8, CYP2C19, and CYP3A4) to inactive (or weakly active) metabolites. The metabolites are glucuronidated and excreted via the kidney and faeces. The acyl glucuronide has been linked to toxicity, either directly by binding to critical intracellular proteins or by eliciting a hypersensitivity response.

References

1. Derry S, Wiffen PJ, Moore RA, *et al*. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database Syst Rev*. 2017;**7**:CD012638.
2. Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. *Br J Anaesth*. 2019;**123**(2):e412–23.

Dihydrocodeine

Standard-release

DF118 Forte® (CD5 POM)
Tablet: 40mg (100).

Generic (CD5 POM)

Tablet: 30mg (28; 30; 100; 500).
Oral solution: 10mg/5mL (150mL).
Injection (CD2 POM): 50mg/mL (10).

Modified-release

DHC Continus® **(***CD5 POM***)**
Tablet: 60mg (56); 90mg (56); 120mg (56).

Combination products

*Certain products containing <10mg dihydrocodeine and paracetamol are available OTC (**CD5 P**).*

Remedeine® **(***CD5 POM***)**

Tablet: dihydrocodeine 20mg/paracetamol 500mg (56; 112).

Remedeine Forte® **(***CD5 POM***)**

Tablet: dihydrocodeine 30mg/paracetamol 500mg (56).

Generic **(***CD5 POM***)**

Tablet (scored): co-dydramol 10/500 (dihydrocodeine 10mg/paracetamol 500mg) (30; 100; 500); co-dydramol 20/500 (dihydrocodeine 20mg/paracetamol 500mg) (56; 112); co-dydramol 30/500 (dihydrocodeine 30mg/paracetamol 500mg) (56).

Indications

- Management of moderate to severe pain.

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care, although there may be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation).
- Dihydrocodeine is contraindicated for use in:
  - acute alcoholism
  - head injury (opioids interfere with pupillary observations)
  - obstructive airways disease
  - paralytic ileus
  - raised intracranial pressure
  - respiratory depression.
- Use dihydrocodeine with caution in the following instances:
  - adrenocortical insufficiency (lower doses recommended)
  - arrhythmias
  - asthma (can release histamine)

- bowel obstruction
- concurrent use with CYP2D6 inhibitors (see ➔ *Drug interactions*, p. 225)
- concurrent administration of MAOIs or within 2 weeks of discontinuation of their use
- COPD
- diseases of the biliary tract (e.g. gallstones)
- elderly (see ➔ *Dose adjustments*, p. 226)
- hepatic impairment (see ➔ *Dose adjustments*, p. 226)
- hypothyroidism (lower doses suggested)
- inflammatory bowel disease
- pancreatitis
- myasthenia gravis
- prostatic hypertrophy
- raised intracranial pressure
- renal impairment (see ➔ *Dose adjustments*, p. 226)
- sleep apnoea (respiratory effects of opioids are more pronounced during sleep).

- Dihydrocodeine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs, SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 225). Dihydrocodeine, like *morphine*, is associated with a low risk; nonetheless, treatment must be reviewed urgently if symptoms develop, dihydrocodeine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of dihydrocodeine and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Avoid abrupt withdrawal as development of physical and/or psychological dependence can occur within 2 weeks of continual use. An abstinence syndrome may be precipitated if dihydrocodeine is suddenly discontinued; it may occur within a few hours after withdrawal and is maximal between 1 and 3 days. Withdrawal symptoms include:
  - abdominal colic
  - anxiety
  - body aches
  - diarrhoea
  - dysphoria
  - flu-like symptoms

- irritability
- mydriasis
- nausea
- restless legs syndrome
- tachycardia
- tremors.

- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

☹ Adverse effects

The frequency is not defined; refer to the SmPC for a full list of adverse effects. Commonly reported adverse effects include the following:

- constipation; dizziness; drowsiness; headache; nausea; pruritus; rash; shortness of breath; vomiting.

Less commonly reported adverse effects include:

- abdominal pain; biliary spasm; confusion; decreased libido; dry mouth; flushing; hallucinations; hypotension; paraesthesia; paralytic ileus; respiratory depression; sweating; ureteric spasm; urinary retention; visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- The major metabolic pathway involves metabolism by CYP3A4 to nordihydrocodeine (similar activity to dihydrocodeine). Dihydrocodeine is also metabolized by CYP2D6 into the active metabolite dihydromorphine, which is subsequently metabolized by glucuronidation to dihydromorphine-6-O-glucuronide. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Note that unlike codeine, interactions between CYP2D6 inhibitors and dihydrocodeine do not appear to reduce analgesic benefit significantly, possibly because the metabolites are produced in such low concentrations as to not have a clinically significant effect.

Pharmacodynamic
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 223.
- *CNS depressants*—risk of excessive sedation.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of dihydrocodeine may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOIs*—risk of severe and unpredictable interactions with MAOIs, involving potentiation of opioid or serotonergic effects.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 223.

Dose

Oral

Standard-release
- 30mg to 60mg PO every 4–6 hours when required. Maximum daily dose 240mg.
- Using *DF118 Forte®*, 40mg to 80mg PO TDS PRN. Maximum daily dose 240mg.

Modified-release
- 60mg to 120mg PO every 12 hours.

Parenteral
- 50mg by SUBCUT or deep IM injection repeated every 4–6 hours.
- ‡Alternatively, 100mg to 200mg via CSCI over 24 hours. Higher doses have been used.

Dose adjustments

Elderly
- No specific guidance is available, although lower starting doses may be preferable. Dose requirements should be individually titrated.

Hepatic/renal impairment
- No specific guidance is available, although in patients with hepatic impairment, the plasma concentration is expected to be increased. Dihydrocodeine is generally not recommended and alternative drugs should be considered.
- No specific guidance is available for patients with renal impairment. However, since metabolites are renally excreted, lower starting doses may be preferable and dose requirements should be individually titrated.

Additional information
- Dihydrocodeine and codeine have traditionally been used, instead of morphine (or alternative), for headache associated with brain metastases. There is no evidence to support this use.

- *DHC Continus*® tablets must be swallowed whole, and not be broken, crushed, or chewed.
- Nausea and vomiting are relatively common and limiting side effects to the use of regular dihydrocodeine alone. This can be overcome by using lower doses more frequently (e.g. 30mg PO 4-hourly) or using modified-release preparation.
- In the absence of a liquid formulation, oral standard-release tablets can be crushed and dispersed in water immediately prior to use.
- Dihydrocodeine is stated to be *physically* compatible under stated conditions with haloperidol and midazolam.[2]

Pharmacology

Dihydrocodeine is a synthetic opioid analgesic with low oral bioavailability, presumably due to first-pass metabolism. It is metabolized in the liver by CYP3A4 (major) to nordihydrocodeine, and by CYP2D6 (minor) to dihydromorphine, which may add to its analgesic effect. Unchanged drug plus metabolites are renally excreted.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
2. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Docusate sodium

*Diocty*l® *(P)*
Capsule: 100mg (30; 100).
Dulcoease (P)

Generic (P)
Oral solution (sugar free): 12.5mg/5mL (300mL); 50mg/5mL (300mL).

Norgalax Micro-enema® (P)
Enema: 120mg in 10g (6 × 10g).

Indications

- Chronic constipation.

Contraindications and cautions

- SmPCs advises that docusate should not be administered to patients with abdominal pain, nausea, vomiting, or intestinal obstruction.
- Oral solution may contain aspartame—avoid in phenylketonuria (refer to individual SmPCs).

Adverse effects

The frequency is not defined; refer to the SmPC for a full list of adverse effects. Reported adverse effects include:

- abdominal cramps; burning sensation in the mouth (oral solution only—drink with plenty of water or flavoured drink); diarrhoea; nausea; skin rash.

Drug interactions

Examples of potential interactions are shown below. Refer to individual SmPCs for further information.

Pharmacokinetic

- *Mineral oils (e.g. liquid paraffin)*—increased risk of toxicity through enhanced absorption.

Pharmacodynamic

- *Anticholinergics*—antagonize the laxative effect.
- *Cyclizine*—antagonizes the laxative effect.
- *Opioids*—antagonize the laxative effect.
- *5-HT$_3$ antagonists*—antagonize the laxative effect.
- *TCAs*—antagonize the laxative effect

Dose

Oral

- Initial dose 100mg PO BD, increased as necessary according to response, to a usual maximum of 200mg PO TDS.[+]
- Licensed maximum dose is 500mg/day in divided doses.

Rectal

- Usual dose 120mg OD (one enema). It can be repeated on the same or next day.

Dose adjustments

Elderly

- No specific recommendations.

Hepatic/renal impairment

- No specific recommendations.

Additional information

- Oral preparation can take up to 72 hours to work; enema usually works within 20 minutes.

Pharmacology

Docusate sodium is a surfactant and used as a faecal softening agent. It works by allowing water to penetrate faeces, allowing them to soften. It is believed to have a mild stimulant action, particularly at higher doses.

Domperidone ♥

Motilium® (POM)
Tablet: 10mg (30; 100).

Generic (POM)
Tablet: 10mg (30; 100).
Oral suspension: 5mg/5mL (200mL).

Indications

- Nausea and vomiting.
- [+]Gastro-oesophageal reflux.
- [+]GI dysmotility (e.g. belching, bloating).

Contraindications and cautions

- Contraindicated for use in patients with:
  - bowel obstruction or perforation
  - co-administration with potent CYP3A4 inhibitors (see ➔ *Drug interactions*, p. 231)
  - GI haemorrhage
  - moderate or severe hepatic impairment (see ➔ *Dose adjustments*, p. 231)
  - prolactinoma.
- In addition, there is a *known* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 231)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - do not use in conditions where cardiac conduction is, or could be, impaired with an increased risk of ventricular arrhythmia (e.g. congestive heart failure, QT prolongation, significant electrolyte disturbances).
- Avoid grapefruit juice (see ➔ *Drug interactions*, p. 231).
- Domperidone has been associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. Risk factors include age (>60 years), doses >30mg, and concurrent use of QT-prolonging drugs or CYP3A4 inhibitors.
- Dose reductions are necessary in patients with renal impairment (see ➔ *Dose adjustments*, p. 231).
- Patients should be counselled to stop taking domperidone and seek medical help, should any cardiac symptoms develop.

Adverse effects

Adverse effects are likely to be more frequent with higher doses and longer duration of treatment. Refer to the SmPC for a full list of adverse effects.

- *Common*: dry mouth.
- *Uncommon*: anxiety; asthenia; breast discomfort; diarrhoea; drowsiness; headache; hyperprolactinaemia (with associated symptoms, e.g. galactorrhoea, gynaecomastia, amenorrhoea); intestinal cramps; loss of libido; pruritus; rash.

- *Not known*: agitation; extrapyramidal effects; gynaecomastia; abnormal LFTs; nervousness; QT prolongation; TdP; urinary retention; urticaria; ventricular arrhythmias.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Domperidone is a substrate of a variety of cytochromes such as CYP3A4 (major pathway), CYP1A2, CYP2B6, and CYP2D6.
- Co-administration with CYP3A4 inhibitors (see *Inhibitors* on the inside back cover) may increase peak plasma concentrations of domperidone, which could lead to increases in the QT interval. Concomitant use with strong CYP3A4 inhibitors, such as clarithromycin, erythromycin, and itraconazole, is contraindicated by the manufacturer. Refer to the SmPC for further details.
- Conversely, co-administration with CYP3A4 inducers (see *Inducers* on the inside back cover) may reduce the effectiveness of domperidone.
- Avoid grapefruit juice, as it may increase the bioavailability of domperidone through inhibition of intestinal CYP3A4.

Pharmacodynamic

- Domperidone can cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see *Contraindications and cautions*, p. 230). Refer to the SmPC for further details.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticholinergics*—may antagonize the prokinetic effect.
- *Cyclizine*—may antagonize the prokinetic effect.
- *Opioids*—antagonize the prokinetic effect.
- *5-HT$_3$ antagonists*—antagonize the prokinetic effect.
- *TCAs*—may antagonize the prokinetic effect.

Dose

Due to a perceived increased risk of arrhythmia in patients >60 years old receiving doses >30mg/day, the maximum licensed dose (for nausea and vomiting) is now 10mg PO TDS, which usually should not exceed 7 days. See *Additional information*, p. 232.

If necessary, the following doses (for all indications) may be used:

- †by mouth, 10mg to 20mg TDS to QDS; maximum daily dose of 80mg
- consider using metoclopramide before using these doses.

Dose adjustments

Elderly

- No specific guidance is available, but the dose should be carefully adjusted to individual requirements.

Hepatic/renal impairment

- Domperidone is contraindicated for use in patients with moderate or severe hepatic impairment. No dose adjustments are necessary for patients with mild hepatic impairment.
- In patients with severe renal impairment (CrCl <10mL/min), the dosing frequency should be reduced to OD or BD with repeated use. Dose adjustments are unnecessary for single administration.

Additional information

- Based on the results of two 'thorough QT' studies (the gold standard for assessment of QT prolongation), domperidone does not appear to be strongly associated with QT prolongation at doses of 20mg PO QDS in *healthy* volunteers. There are, however, limited case reports that support an association with cardiac dysfunction in patients with a higher baseline risk of QT prolongation. Presently, the risk of QT prolongation remains unknown. A decision to use higher than licensed doses can be made with this in mind.
  - If necessary, the tablets can be crushed before administration if the suspension is unavailable.

Pharmacology

Domperidone is a peripheral D_2 receptor antagonist and does not usually cross the blood–brain barrier. The cardiotoxicity of domperidone may be explained by a concentration-dependent block of the hERG channel, in addition to inhibition of cardiac Na^+ channels, including $NaV_{1.5}$, an action similar to that displayed by local anaesthetics. Domperidone undergoes extensive first-pass metabolism (CYP3A4), and metabolites are inactive. Its antiemetic effect is due to two distinct effects: a prokinetic effect and dopamine blockade in the chemoreceptor trigger zone (CTZ), which lies outside the blood–brain barrier. Age (reduced numbers of dopamine receptors, absorption, distribution, metabolism, and excretion (ADME) changes) and polymorphisms of certain genes (e.g. *KCNH2*, *ADRA1D*) can influence the effect and toxicity of domperidone.

Donepezil ♥

Aricept® (POM)

Tablet: 5mg (28); 10mg (28).

Aricept® Evess (POM)

Orodispersible tablet: 5mg (28); 10mg (28).

Generic (POM)

Tablet: 5mg (28); 10mg (28).
Orodispersible tablet: 5mg (28); 10mg (28).
Oral solution: 1mg/mL (150mL).

Indications

- Symptomatic treatment of mild to moderately severe Alzheimer's dementia.
- †Cognitive impairment of vascular disease of the brain.[1]
- †Dementia in Parkinson's disease (see ➔ *Additional information*, p. 234).[2]

Contraindications and cautions

- Despite the *CredibleMeds® known* risk of dose-related QT prolongation/TdP with donepezil, there are no warnings of such in the UK SmPC. Nonetheless:
  - do not prescribe for patients taking drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 234)
  - do not prescribe for patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - do not use doses above 40mg (or 20mg in the elderly) unless recommended by a specialist
  - use with caution in patients with significant bradycardia and those with recent acute myocardial infarction or uncompensated heart failure.
- Donepezil should be used with caution in the following:
  - asthma
  - COPD
  - severe hepatic impairment
  - supraventricular conduction abnormalities (may cause bradycardia)
  - susceptibility to peptic ulcers (may increase gastric acid secretion) (see ➔ *Drug interactions*, p. 234).
- Certain orodispersible formulations contain aspartame (refer to individual SmPCs). Avoid use in patients with phenylketonuria.
- All patients receiving donepezil should have their ability to continue driving or operating complex machines evaluated. Refer to ➔ Chapter 2, *Drugs and driving*, p.41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: diarrhoea; headache; nausea.

- *Common*: abnormal dreams; aggression; agitation; anorexia; common cold; dizziness; fatigue; hallucinations; insomnia; muscle cramps; rash; sweating; urinary incontinence; vomiting.
- *Uncommon*: bradycardia; GI haemorrhage; hypersalivation; peptic ulcer.
- *Rare*: atrioventricular block; extrapyramidal reactions; hepatitis; liver dysfunction; sinoatrial block.
- *Very rare*: neuroleptic malignant syndrome; rhabdomyolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Donepezil is metabolized by CYP3A4 and CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of donepezil through inhibition of intestinal CYP3A4.

Pharmacodynamic

- Donepezil is associated with a known risk of prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 233).
- *Anticholinergics*—may antagonize the effects.

Dose

- Initial dose 5mg PO ON, prior to retiring. The dose can be increased, if necessary, after 1 month to a maximum of 10mg PO ON.

Dose adjustments

Elderly

- Usual adult doses can be used.

Hepatic/renal impairment

- For patients with mild to moderate hepatic impairment, dose escalation should be performed according to individual tolerability. There is no recommendation for use in severe hepatic disease.
- Usual adult doses can be used in renal impairment.

Additional information

- *Rivastigmine* is licensed for the treatment of Parkinson's disease dementia.
- Tablet can be dispersed in water immediately prior to administration if the oral solution or orodispersible tablet are unavailable.

Pharmacology

Donepezil is a centrally acting specific and reversible inhibitor of acetylcholinesterase. Its therapeutic effect is through enhancement of cholinergic function. It is well absorbed, with a relative oral bioavailability of 100%. It is metabolized by CYP3A4 and CYP2D6, as well as undergoing glucuronidation. The main metabolite has similar activity to donepezil. Approximately 17% of the dose is excreted unchanged in the urine.

References

1. Perng CH, Chang YC, Tzang RF. The treatment of cognitive dysfunction in dementia: a multiple treatments meta-analysis. *Psychopharmacology (Berl)*. 2018;**235**(5):1571–80.
2. Dubois B, Tolosa E, Katzenschlager R, *et al*. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. *Mov Disord*. 2012;**27**(10):1230–8.

Duloxetine

Cymbalta® (POM)

Capsule (gastro-resistant): 30mg (28); 60mg (28).

Generic (POM)

Capsule (gastro-resistant): 30mg (28); 60mg (28).

Certain gastro-resistant capsule formulations (20mg; 40mg) are licensed for stress incontinence in women and not discussed further.

Indications

- Major depressive episodes.
- Generalized anxiety disorder.
- Diabetic peripheral neuropathic pain in adults.
- ‡Non-diabetic neuropathic pain.[1]

Contraindications and cautions

- Duloxetine is contraindicated in the following conditions:
  - co-administration with potent CYP1A2 inhibitors (see ➔ *Drug interactions*, p. 238)
  - co-administration with an irreversible MAOI (including *rasagiline* and *selegiline*) or within 14 days of stopping one
  - at least 5 days should be allowed after stopping duloxetine before starting an irreversible MAOI
  - moderate to severe hepatic impairment
  - severe renal impairment (CrCl <30mL/min)
  - uncontrolled hypertension (noradrenergic effect of duloxetine can cause clinically significant hypertension).
- Combination with selective reversible MAOIs (e.g. *linezolid*, *moclobemide*) is not recommended, although the SmPC offers no specific advice. In exceptional circumstances, under specialist guidance, *linezolid* may be given with duloxetine, but the patient must be closely monitored for symptoms of serotonin toxicity.
- Serotonin toxicity has been reported in patients using duloxetine (see ➔ Chapter 1, *Serotonin toxicity*, p. 29). Treatment should be reviewed immediately if this is suspected, duloxetine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated. If treatment with duloxetine and other serotonergic drugs is clinically warranted, close observation of the patient is advised (see ➔ *Drug interactions*, p. 238).
- There is a risk of haemorrhage with duloxetine. Use with caution in patients using anticoagulants and drugs with an antiplatelet action, e.g. aspirin, NSAIDs (see ➔ *Drug interactions*, p. 238).
- Use with caution in epilepsy, as there is limited experience (may rarely lower the seizure threshold). *SSRIs* are considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.
- Use with caution in:
  - bipolar disorder
  - diabetes (may alter glycaemic control)

  - elderly (greater risk of hyponatraemia)
  - glaucoma (may cause mydriasis)
  - hypertension
  - severe renal impairment
  - thrombocytopenia (risk of haemorrhage).
- BP monitoring is recommended, particularly during the first month of treatment, for patients with known hypertension and/or other cardiac disease because duloxetine is associated with an increase in BP. If there is a sustained increase in BP, dose reduction or gradual discontinuation should be considered.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Abrupt discontinuation should be avoided due to the risk of withdrawal reactions, e.g. agitation, anxiety, diarrhoea, dizziness, drowsiness, fatigue, headache, hyperhidrosis, nausea and/or vomiting, sensory disturbances (including paraesthesia), and sleep disturbances. When stopping treatment, the dose should be reduced gradually over at least 1–2 weeks. See ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- May precipitate psychomotor restlessness, which usually appears during early treatment. The use of duloxetine should be reviewed.
- Duloxetine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: drowsiness; dry mouth; headache; nausea.
- *Common*: abdominal pain; agitation; anxiety; reduced appetite; BP increase; blurred vision; constipation; diarrhoea; dizziness; dyspepsia; dysuria; fatigue; flatulence; flushing; insomnia; lethargy; musculoskeletal pain; palpitations; paraesthesia; rash (acneiform reported—treat as acne or withdraw the drug); sexual dysfunction (e.g. abnormal orgasm, reduced libido); sleep disturbances (including abnormal dreams); sweats (less commonly night sweats or cold sweats); tinnitus (also on withdrawal); tremor; vomiting; weight loss; yawning.
- *Uncommon*: abnormal bleeding (bruising, epistaxis); akathisia; altered taste; atrial fibrillation; bruxism; dry eye; dyskinesia; dysphagia; ear pain; gastritis; GI haemorrhage; hepatitis; hyperglycaemia (especially in diabetic patients); hypertension; hypotension (postural hypotension reported during initiation); laryngitis; raised liver enzymes; mydriasis; myoclonus; restless legs syndrome; suicidal ideation; syncope; tachycardia; urinary symptoms (e.g. hesitation, retention); urticaria; vertigo; visual disturbances; weight increase.

- *Rare*: aggression; anaphylaxis; convulsions; dehydration; extrapyramidal reactions; glaucoma; hallucinations; hepatic impairment (including jaundice); hyperprolactinaemia; hypertensive crisis; hypothyroidism; psychomotor restlessness; serotonin syndrome (see ➔ *Drug interactions*); SIADH/hyponatraemia; Stevens–Johnson syndrome; stomatitis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Duloxetine is a moderate inhibitor of CYP2D6; it is a substrate of CYP1A2 and CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Smokers may have almost 50% lower plasma concentrations of duloxetine (CYP1A2 induction), compared with non-smokers. Dosage adjustments may be necessary upon smoking cessation (see Box 1.11). Co-administration of CYP1A2 inducers (see ➔ *Inducers* on the inside back cover) may lead to reduced duloxetine concentrations, although the clinical significance is unknown. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary.
- Co-administration of duloxetine with potent inhibitors of CYP1A2 (e.g. *amiodarone*, *ciprofloxacin, fluvoxamine*— see ➔ *Inhibitors* on the inside back cover) is likely to result in higher concentrations of duloxetine (see ➔ *Contraindications and cautions*, p. 236).
- Be mindful of CYP2D6 inhibition when switching antidepressants (see ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74).

Pharmacodynamic

- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 236)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SSRIs*, *TCAs*, *tapentadol*, *tramadol*, *trazodone*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.
- *Antidiabetics*—impaired glycaemic control (risk of hyperglycaemia).
- *Antiplatelet agents*—potential increased risk of bleeding.
- *CNS depressants*—additive sedative effect.
- *Cyproheptadine*—may inhibit the effects of duloxetine.
- *Diuretics*—increased risk of hyponatraemia.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).

- *NSAIDs*—increased risk of bleeding (potentially worse with aspirin and naproxen).
- *SSRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

Major depressive episodes

- Initial and maintenance dose 60mg PO OD with or without food. There is no evidence to suggest that 120mg PO daily offers any therapeutic advantage.

Generalized anxiety disorder

- Initial dose 30mg PO OD with or without food. Doses can be increased, as necessary, to a usual maintenance dose of 60mg PO OD with or without food. Further dose increases up to 90mg or 120mg may be considered, based upon clinical response.

Diabetic peripheral neuropathic pain/$^{+}$*non-diabetic neuropathic pain*

- Initial dose 60mg PO OD with or without food.
- Some patients may benefit from a lower initial dose of 30mg PO OD^{+}.
- The plasma concentration of duloxetine displays large interpatient variation (see ➔ *Pharmacology*). Patients who respond inadequately to 60mg PO OD may benefit from doses of up to 60mg PO BD.

Dose adjustments

Elderly

- Dosage reductions not necessary.

Hepatic/renal impairment

- Duloxetine is not recommended for use in patients with moderate to severe hepatic impairment.
- No dosage adjustment is necessary for patients with mild or moderate renal impairment (CrCl ≥30mL/min). Duloxetine is contraindicated in patients with severe renal impairment (CrCl <30mL/min).

Additional information

- Antidepressant therapeutic response is usually seen after 2–4 weeks of treatment.
- In the treatment of anxiety, duloxetine should be continued for several months after therapeutic response in order to prevent relapse.
- For neuropathic pain, response to treatment should be evaluated after 2 months. If the patient has not responded after this time, benefit is unlikely and duloxetine should be gradually withdrawn. Patients who respond should be reassessed regularly, at least every 3 months.

Pharmacology

Although the exact mechanisms of the antidepressant and analgesic actions of duloxetine are unknown, they are believed to be related to its

potentiation of serotonergic and noradrenergic activity in the CNS. Duloxetine is a combined SNRI, with weak inhibition of dopamine reuptake.

Duloxetine is extensively metabolized by CYP1A2 and CYP2D6, followed by conjugation; two major, but inactive, metabolites are formed, which are excreted mainly renally. The pharmacokinetics of duloxetine demonstrate large interpatient variation, due to, in part, gender, age, smoking status, and CYP2D6 metabolizer status.

Reference

1. Finnerup NB, Attal N, Haroutounian S, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;**14**(2):162–73.

Edoxaban

Lixiana® (POM)
Tablet: 15mg (*orange*—10); 30mg (*pink*—28); 60mg (*yellow*—28).

Indications

- Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischaemic attack.
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

Contraindications and cautions

- Edoxaban is contraindicated for use in the following circumstances:
  - active clinically significant bleeding
  - at risk of a major bleed (e.g. GI ulceration—current or recent, presence of malignant neoplasms at high risk of bleeding)
  - concomitant treatment with any other anticoagulants, except under specific circumstances or switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter)
  - hepatic disease associated with coagulopathy and clinically relevant bleeding risk
  - hypertension (severe uncontrolled).
- Edoxaban is not recommended for use in patients with end-stage renal disease (CrCl <15mL/min) or severe hepatic impairment (see *Dose adjustments*, p. 243).
- Concomitant use of edoxaban with aspirin in the elderly should be done with caution due to an increased risk of bleeding.
- For instructions on management of bleeding—see the current edition of the *BNF*.
- Use with caution in:
  - combination with P-gp inhibitors/inducers (see *Drug interactions*, p. 242)
  - concomitant use of medicines affecting haemostasis (see *Drug interactions*, p. 242)
  - mild to moderate hepatic impairment (see *Dose adjustments*, p. 243)
  - prosthetic heart valves (efficacy not established)
  - moderate to severe renal impairment (see *Dose adjustments*, p. 243).
- Edoxaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; anaemia; dizziness; epistaxis; headache; haematuria; haemorrhage (GI, soft tissue, vaginal); raised LFTs; nausea; pruritus; rash.

- *Uncommon*: haemorrhage (brain, conjunctival, intraocular, scleral); haemoptysis; hypersensitivity; thrombocytopenia; urticaria.
- *Rare*: allergic oedema; anaphylaxis; haemorrhage (intramuscular, pericardial, retroperitoneal, subarachnoid).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Edoxaban is a substrate for P-gp and a minor metabolic pathway involving CYP3A4/5. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Refer to the SmPC for full information about interactions with P-gp inhibitors.
- *P-gp inhibitors*—concomitant treatment with *ciclosporin*, *dronedarone*, *erythromycin*, or *ketoconazole* requires a dose reduction to 30mg PO OD; co-administration with *quinidine*, *verapamil*, or *amiodarone does not* require a dose reduction; other P-gp inhibitors have not been studied.
- *P-gp inducers*—use with caution as efficacy may be compromised.
- The effect of *grapefruit juice* is unknown.

Pharmacodynamic

- Refer to the SmPC for specific information relating to the bleeding risk/interaction with the following drugs:
  - *aspirin* (concurrent use with aspirin 75mg is acceptable; use higher doses cautiously)
  - *clopidogrel*
  - *corticosteroids*
  - *NSAIDs*
  - *SSRIs/SNRIs*.

Dose

The manufacturer recommends that LFTs and urea and electrolytes (U&Es) are performed prior to initiating edoxaban.

Prevention of stroke and systemic embolism

- 60mg PO OD.

Treatment of DVT and PE, and prevention of recurrent DVT and PE

- 60mg PO BD for at least 5 days.
  - Treatment duration of at least 3 months should be considered if DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma).
  - Extended durations should be based on permanent risk factors.

For *both* NVAF and VTE, patients with body weight ≤60kg or CrCl 15–50mL/min or receiving P-gp inibitors (*the SmPC specifies ciclosporin, dronedarone, erythromycin, or ketoconazole, but seek advice for other strong P-gp inhibitors*), the recommended dose is 30mg PO OD.

Dose adjustments

Elderly

- Dose adjustments are unnecessary based on age alone.

Hepatic/renal impairment

- Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Use in patients with severe hepatic impairment is not recommended.
- Dose adjustments are not required in patients with mild or moderate hepatic impairment.
- The manufacturer advises a dose reduction to 30mg PO OD in patients with moderate to severe renal impairment (CrCl 15–50mL/min).
- Dose adjustments are not required in patients with mild renal impairment.
- Use is not recommended in patients with CrCl <15mL/min or those on dialysis, due to lack of clinical data.

Additional information

- Tablets may be crushed and mixed with water or apple juice/puree immediately prior to use and administered orally. The crushed tablet can also be given in 60mL of water and given immediately via a nasogastric tube, which should be flushed after administration.
- Refer to the SmPC for information about changing from, or to, other anticoagulants.

Pharmacology

Edoxaban is a highly selective direct factor Xa inhibitor. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathways of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Edoxaban has an oral bioavailability of approximately 62%. It is a substrate of P-gp. It is metabolized to three active metabolites by hydrolysis (via carboxylesterase 1), conjugation, and CYP3A4/5 (<10%). The main metabolite reaches <10% of the parent compound. Renal excretion accounts for approximately 35% of total clearance.

Enoxaparin

Clexane® (POM)

Injection (*single-dose syringe for SUBCUT use*): 20mg (0.2mL, 2000 units); 40mg (0.4mL, 4000 units); 60mg (0.6mL, 6000 units); 80mg (0.8mL, 8000 units); 100mg (1mL, 10,000 units).

Clexane® Forte (POM)

Injection (*single-dose syringe for SUBCUT use*): 120mg (0.8mL, 12,000 units); 150mg (1mL, 15,000 units).

Clexane® Multidose (POM)

Injection (*multi-dose vial*): 300mg (3mL, 30,000 units).

Enoxaparin BECAT® (POM)

Injection (*single-dose syringe for SUBCUT use*): 20mg (0.2mL, 2000 units); 40mg (0.4mL, 4000 units); 60mg (0.6mL, 6000 units); 80mg (0.8mL, 8000 units); 100mg (1mL, 10,000 units).

Inhixa® (POM)

Injection (*single-dose syringe for SUBCUT use*): 20mg (0.2mL, 2000 units); 40mg (0.4mL, 4000 units); 60mg (0.6mL, 6000 units); 80mg (0.8mL, 8000 units); 100mg (1mL, 10,000 units).

Indications

- Treatment and prophylaxis of DVT and PE.
- Other indications apply but are not normally relevant in palliative care (refer to the SmPC).

Contraindications and cautions

- Enoxaparin is contraindicated for use in patients with:
  - active gastric or duodenal ulceration
  - history of heparin-induced thrombocytopenia within the past 100 days or in the presence of circulating antibodies
  - malignant neoplasm at high risk of bleeding
  - oesophageal varices
  - recent haemorrhagic stroke (should not be used within 14 days)
  - spinal anaesthesia (treatment doses)
  - surgery.
- Use with caution in patients with an increased risk of bleeding complications and seek specialist advice if necessary:
  - acute infective endocarditis (risk of cerebral haemorrhage)
  - brain tumours (increased risk of intracranial bleeding)
  - concurrent use of anticoagulant/antiplatelet agents/NSAIDs (see *Drug interactions*, p. 245)
  - diabetes mellitus (increased risk of hyperkalaemia and metabolic acidosis)
  - hepatic impairment (see *Dose adjustments*, p. 247)
  - history of peptic ulcer
  - low weight (increased risk of bleeding)
  - mechanical prosthetic heart valves
  - obesity (increased risk of thromboembolism)

  - recent ischaemic stroke
  - retinopathy (hypertensive or diabetic)
  - severe arterial hypertension
  - severe renal impairment (see ➔ *Dose adjustments*, p. 247)
  - spinal anaesthesia (thromboprophylaxis doses)
  - thrombocytopenia (platelet count $<75 \times 10^9$).
- A baseline platelet count should be taken prior to initiating treatment, and monitored closely during the first 3 weeks (e.g. every 2–4 days) and regularly thereafter. If a confirmed significant decrease of the platelet count is observed (30–50% of the initial value), enoxaparin must be discontinued.
- Enoxaparin must not be administered by IM injection—risk of injection site haematoma.
- Advice should be sought from anaesthetic colleagues if considering an epidural intervention in a patient receiving enoxaparin, due to the risk of spinal haematoma.
- LMWH can inhibit aldosterone secretion, which can cause hyperkalaemia. Patients with pre-existing renal impairment are more at risk (and may include diabetic patients). K^+ should be measured in at-risk patients prior to starting LMWH and monitored regularly thereafter, especially if treatment is prolonged beyond 7 days.
- *Prophylactic doses of enoxaparin are not sufficient to prevent valve thrombosis in patients with prosthetic heart valves.*

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: increased liver enzymes.
- *Common*: erythema at injection site; haemorrhage; haemorrhagic anaemia; headache; hypersensitivity; injection site reaction (haemorrhage; haematoma; inflammation; oedema; pain); pruritus; thrombocytopenia; thrombocytosis; urticaria.
- *Uncommon*: bullous dermatitis; hepatocellular liver injury; skin necrosis at injection site (discontinue).
- *Rare*: alopecia (with prolonged use—usually transient); anaphylactic reactions; eosinophilia; hyperkalaemia (more likely to occur with prolonged duration of treatment and/or in patients with diabetes mellitus or chronic renal failure); hypoaldosteronism; immunologically mediated heparin-induced thrombocytopenia; injection site nodules (resolve after a few days; do not require discontinuation); osteoporosis (long-term treatment).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None recognized.

Pharmacodynamic

- Drugs with anticoagulant or antiplatelet effect may enhance the effect of enoxaparin:
  - *aspirin*

  - *clopidogrel*
  - *dipyridamole*
  - *NSAIDs*.
- *ACE-Is*—increased risk of hyperkalaemia.
- *Amiloride*—increased risk of hyperkalaemia.
- *Antihistamines*—possibly reduce anticoagulant effect.
- *Ascorbic acid*—possibly reduces anticoagulant effect.
- *Corticosteroids*—increased risk of GI bleeding.
- *Spironolactone*—increased risk of hyperkalaemia.
- *SSRIs*—increased risk of bleeding.

Dose

Refer to Haematology for advice if platelets are below 75 × 10^9/L or body weight <40kg or >150kg.

Treatment of DVT and PE in patients with low risk of recurrence
- 1.5mg/kg (or 150 units/kg) SUBCUT OD.

Treatment of DVT and PE in patients with risk factors such as those with obesity, symptomatic PE, cancer, and recurrent VTE
- 1mg/kg (100 units/kg) SUBCUT BD.

Prophylaxis of DVT and PE
- For medical prophylaxis (including immobile cancer patients)—40mg (4000 units) SUBCUT OD. The duration of treatment depends upon risk factors identified (e.g. immobile inpatients may be considered for treatment from admission until discharge), but treatment should continue for at least 6–14 days, whatever the recovery status. Graduated compression stockings should be considered if LMWH is contraindicated.
- Dose adjustments, based on weight, are suggested:
  - <50 kg—use 20mg SUBCUT OD
  - 100kg to 150 kg—use 80mg SUBCUT OD (or [+]40mg SUBCUT BD in high-risk patients)
  - >150kg—use 120mg SUBCUT OD (or [+]60mg SUBCUT BD in high-risk patients).

For surgical prophylaxis
- Moderate risk—20mg (2000 units) SUBCUT at least 2 hours before procedure and each day for at least 7–10 days or longer (until mobilized)
- High risk—40mg (4000 units) SUBCUT 12 hours before procedure and each day for 7–10 days or longer (e.g. up to 4 weeks in cancer patients undergoing abdominal or pelvic surgery).

[+]*Long-distance air travel*
- Cancer patients are at risk of developing VTE during long-distance air travel (considered >6 hours).
- Supply the patient with sufficient quantities to cover flights and provide a cover letter for immigration purposes (see ➔ Chapter 2, *Travelling abroad with medicines*, p. 39).

- 40mg (4000 units) SUBCUT 2–4 hours prior to flight. Should there be long-distance connections, only administer another dose if the following flight is >24 hours after the previous dose (e.g. following a stopover).

Dose adjustments

Elderly

- Usual adult doses recommended.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. The SmPC advises caution due to an increased risk of bleeding.
- Dosage adjustments are unnecessary in patients with mild to moderate renal impairment, although careful monitoring is recommended. Dosage adjustments in patients with renal impairment *must* be based on CrCl, *not* estimated glomerular filtration rate (eGFR). In severe renal impairment (CrCl 15–30mL/min) where 1.5mg/kg SUBCUT OD is indicated as a treatment dose, this should be reduced to 1mg/kg SUBCUT OD, and for prophylaxis, 40mg SUBCUT OD should be reduced to 20mg SUBCUT OD. The SmPC states that enoxaparin is not recommended for patients with end-stage renal disease (CrCl <15mL/min), due to lack of data in this population.

Additional information

- Actual body weight and CrCl should be used for dose calculations.
- Measurement of anti-factor Xa levels, in conjunction with the local Haematology department, can help guide the dose of enoxaparin in difficult cases.
- Refer to local guidelines for target anti-factor Xa ranges. As an example, for prophylaxis, the target anti-factor Xa range is 0.2 to 0.4IU/mL. For treatment, the target range is 0.4 to 0.8IU/mL. Check anti-factor Xa level 3–5 hours post-*third* dose, irrespective of dosing frequency.
- Warfarin may be unsuitable for cancer patients who may require long-term treatment with LMWH. Treatment is occasionally continued indefinitely. Enoxaparin is currently unlicensed for extended treatment.
- If switching from enoxaparin to warfarin, patients must continue both until the INR is within the target range. This generally takes 5 days.
- When switching from enoxaparin to a DOAC, the DOAC should be given 0–2 hours before the time that the next scheduled administration of enoxaparin would be due.
- When switching from a DOAC, the first dose of enoxaparin should be given at the time the next DOAC dose would be taken.
- The risk of heparin-induced thrombocytopenia is low with enoxaparin but may occur between the fifth and 21st day following initiation. If there is a 30–50% reduction of the platelet count, LMWH should be stopped.

Pharmacology

Enoxaparin is an LMWH produced from porcine-derived sodium heparin. It acts mainly through its potentiation of inhibition of factor Xa and thrombin by antithrombin. Enoxaparin is eliminated primarily via the kidneys, hence the need for dose adjustments in renal impairment. Local protocols may help to indicate when treatment of palliative care patients with enoxaparin is appropriate.

Enzalutamide ♀

Xtandi® (POM)

Tablet: 40mg (112); 80mg (56).

Indications

- Treatment of adult men with metastatic, hormone-sensitive prostate cancer, in combination with androgen deprivation therapy.
- Treatment of adult men with high-risk, non-metastatic, castration-resistant prostate cancer.
- Treatment of adult men with metastatic, castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy, in whom chemotherapy is not yet clinically indicated.
- Treatment of adult men with metastatic, castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Contraindications and cautions

- Contraindicated for use in women who are or may become pregnant.
- *Should only be initiated by, or under the supervision of, a specialist.*
- Although not mentioned by *CredibleMeds®*, the SmPC states that androgen deprivation therapy may prolong the QT interval (post-marketing experience). There is a possible risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 249)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- Use with caution in the following:
  - epilepsy (seizures reported—see below)
  - drugs metabolized by CYP2C9, CYP2C19, and CYP3A4 (see ➔ *Drug interactions*, p. 249)
  - hepatic and renal impairment (see ➔ *Dose adjustments*, p. 250)
  - recent CV disease (see SmPC for full details).
- There have been rare reports of posterior reversible encephalopathy syndrome in patients receiving enzalutamide. Symptoms include blindness, confusion, headache, seizure, and other visual and neurological disturbances, which may be associated with or without hypertension. Enzalutamide should be discontinued if this condition arises.
- Enzalutamide has been linked to the development of second primary malignancies (e.g. adenocarcinoma of the colon, bladder cancer, bladder transitional cell carcinoma, transitional cell carcinoma). Patients should be advised to contact a healthcare provider if they experience signs of GI bleeding, haematuria, or other urinary symptoms such as dysuria or urgency.

- There have been reports of hypersensitivity reactions to enzalutamide, with symptoms such as rash and oedema of the face, lip, or tongue. Patients should be advised to contact a healthcare provider, should they experience any of these symptoms.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: asthenia; fall; fatigue; fractures; hot flush; hypertension.
- *Common*: amnesia; anxiety; dry skin; dysgeusia; gynaecomastia; headache; ischaemic heart disease; memory impairment; pruritus; restless legs syndrome.
- *Uncommon*: cognitive disorder; leucopenia; neutropenia; seizure; visual hallucination.
- *Unknown*: oedema (e.g. face, lip, tongue); posterior reversible encephalopathy syndrome; QT prolongation; rash; thrombocytopenia.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Enzalutamide is metabolized by CYP2C8 (major) and CYP3A4 (minor); it is a potent inducer of CYP3A4, with lesser effects on CYP2B6, CYP2C9, CYP2C19, and UGT1A1. Enzalutamide also affects several transporter proteins (e.g. P-gp), with uncertain clinical outcomes (*in vitro* data suggest inhibition; however, while there are no *in vivo* data, the SmPC suggests enzalutamide may act as an inducer of, for example, P-gp, potentially reducing the effect of susceptible drugs).
- Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see *Inducers* and *Inhibitors* on the inside back cover) of, these metabolic enzymes and transport proteins may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Enzalutamide has a half-life of 2.8–10.2 days (average of 5.8 days). The effects of enzyme induction may not be apparent until 1 MONTH after starting treatment (effects may occur within 2 weeks). After discontinuation, the effects are likely to persist for a month or possibly longer.*
- *Alfentanil*—risk of reduced analgesic benefit.
- *Carbamazepine*—clinical effect of both drugs may be affected.
- *Clonazepam*—effect of clonazepam may be reduced.
- *Clopidogrel*—combination should be avoided (CYP2C8 inhibitor); if unavoidable, see *Dose*, p. 250.
- *Codeine*—possible reduced analgesic effect (due to CYP3A4 induction).
- *Corticosteroids*—effect of corticosteroids reduced; higher doses necessary (possibly double or more).
- *Fentanyl*—risk of reduced analgesic benefit.
- *Fluconazole*—possible risk of enzalutamide toxicity.
- *Haloperidol*—effect of haloperidol reduced.
- *Levothyroxine*—increased metabolism may precipitate hypothyroidism.
- *Mirtazapine*—effect of mirtazapine may be reduced.

- *Midazolam*—effect of midazolam may be reduced.
- *Modafinil*—effect of modafinil may be reduced.
- *Oxycodone*—possible risk of reduced analgesic benefit.
- *Rifampicin*—effect of enzalutamide may be reduced.
- *Tramadol*—reduced analgesic effect (due to CYP3A4 induction).
- *Warfarin*—the SmPC states co-administration should be avoided; if used together, regular INR monitoring should be performed.

Pharmacodynamic

- Androgen deprivation therapy may prolong the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.

Dose

- 160mg PO OD.
- Refer to the SmPC for necessary dose adjustments, should the patient develop adverse reactions.
- If concurrent use with a CYP2C8 inhibitor is unavoidable, the dose should be reduced to 80mg PO OD.

Dose adjustments

Elderly

- Usual adult doses recommended.

Hepatic/renal impairment

- Dose adjustments are not required for patients with mild, moderate, or severe hepatic impairment (Child–Pugh class A, B, or C), although the half-life may be increased, possibly related to increased tissue distribution. Although the clinical significance is unknown, the time to maximum pharmacological effect may be increased, as will the consequential effects on CYP enzyme induction during initiation and discontinuation.
- Dose adjustments are not required for patients with mild or moderate renal impairment. The SmPC advises caution in patients with severe renal impairment or end-stage renal disease, due to lack of data. Dialysis is unlikely to significantly remove enzalutamide.

Pharmacology

Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. It also competitively inhibits androgen binding to androgen receptors. The net effect is a reduction in the growth of prostate cancer cells, tumour cell death, and tumour regression. Enzalutamide is well absorbed (84.2%), with a mean half-life of 5.8 days (range 2.8–10.2 days). Steady state is achieved in approximately 1 month after initiation. It is extensively metabolized by CYP2C8 (major) and CYP3A4/5, producing two metabolites: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). N-desmethyl enzalutamide is equally as active as enzalutamide. Elimination is primarily renal (mainly inactive metabolite), with biliary excretion occurring for small amounts.

Escitalopram ♥

Cipralex® (POM)
Tablet: 5mg (28); 10mg (28); 20mg (28).
Oral drops (sugar-free): 20mg/mL (15mL) (*20mg = 20 drops*).

Generic (POM)
Tablet: 5mg (28); 10mg (28); 20mg (28).

Indications

- Generalized anxiety.
- Depression.
- Panic.
- Social anxiety (not discussed).
- Obsessive–compulsive disorder (not discussed).

Contraindications and cautions

- Do not use with an irreversible MAOI or within 14 days of stopping one. At least 7 days should elapse after discontinuing escitalopram treatment before starting a MAOI.
- The combination of escitalopram with *reversible* MAO-A inhibitors (e.g. *moclobemide*) or the *reversible, non-selective* MAO-inhibitor *linezolid* is contraindicated. If it is essential to use these drugs in combination with escitalopram, the patient must be closely monitored for symptoms of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) such as hypertension, cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- Although the combination of the MAO-B selective inhibitors *rasagiline* and *selegiline* with SSRIs is well tolerated, there have been case reports of serotonin toxicity. If such a combination is necessary, the recommendation is to use *citalopram* or *sertraline* without exceeding recommended doses.[1]
- There is a *known* risk of dose-dependent QT prolongation/TdP:
  - do not prescribe for patients taking drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 253)
  - do not prescribe for patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - use with caution in patients with significant bradycardia and those with recent acute myocardial infarction or uncompensated heart failure.
- Serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) has been reported in patients using SSRIs. Escitalopram should be discontinued immediately if this is suspected and supportive symptomatic treatment should be initiated. Escitalopram should not be used concomitantly with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 253).
- Use with caution in epilepsy. SSRIs are, however, considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.

- In addition, use with caution in:
  - diabetes (SSRIs can alter glycaemic control and may cause impaired awareness of hypoglycaemia)
  - elderly (greater risk of hyponatraemia)
  - hepatic/renal impairment (see *Dose adjustments*, p. 254)
  - glaucoma (may cause mydriasis).
- The SmPC makes a specific recommendation about CYP2C19 poor metabolizers (see *Dose adjustments*, p. 254). Note that development of adverse effects is not a predictor of genetic status.
- Akathisia/psychomotor restlessness may occur within the first few weeks of treatment (consider discontinuing).
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Escitalopram may increase the risk of haemorrhage. Use with caution in patients with bleeding disorders or concurrent use with other drugs carrying a similar risk (see *Drug interactions*, p. 253).
- Some patients may experience increased anxiety symptoms at the beginning of treatment. This paradoxical reaction usually subsides within 2 weeks during continued treatment. A low starting dose is advised to reduce the likelihood of this effect.
- There is an increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs. The mechanism is unknown.
- Avoid abrupt withdrawal as symptoms such as agitation, anxiety, dizziness, nausea, sleep disturbance (e.g. insomnia, intense dreams), and tremor can occur. Although generally mild, they can be severe in some patients. Withdrawal symptoms usually occur within the first few days of discontinuing treatment and they usually resolve within 2 weeks, though they can persist in some patients for up to 3 months or longer. See Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: headache; nausea.
- *Common*: anxiety; decreased appetite; increased appetite; arthralgia; constipation; diarrhoea; dizziness; abnormal dreams; drowsiness; dry mouth; fatigue; insomnia; myalgia; paraesthesia; restlessness; sexual dysfunction (anorgasmia—female, ejaculation failure, impotence, decreased libido); sinusitis; increased sweating; tremor; vomiting; increased weight; yawning.
- *Uncommon*: agitation; alopecia; bruxism; confusion; dysgeusia; haemorrhage (e.g. epistaxis, GI); menorrhagia; mydriasis (may lead to

glaucoma); oedema; rash; panic attack; pruritus; rash; sexual dysfunction (increased libido); sleep disorder; syncope; tachycardia; tinnitus; urticaria; decreased weight; visual disturbance.
- *Rare*: aggression; anaphylaxis; bradycardia; depersonalization; hallucinations; serotonin syndrome.
- *Unknown*: akathisia; angioedema; anorexia; bone fractures; convulsions; dyskinesia; ecchymosis; galactorrhoea; hepatitis; hyponatraemia; abnormal LFTs; mania; postural hypotension; priapism; psychomotor restlessness; QT prolongation/TdP (associated predominantly in female patients, with hypokalaemia or pre-existing cardiac conditions); SIADH; suicidal behaviour; thrombocytopenia; urinary retention.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Escitalopram is a major substrate of CYP2C19 (see ➔ *Dose adjustments*, p. 254), with some metabolism catalysed by CYP2D6 and CYP3A4; it is also an inhibitor of CYP2D6 and a weak inhibitor of CYP2C19. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.
- Be mindful of CYP2D6 inhibition when switching antidepressants (see ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74).
- *Esomeprazole*—plasma concentration of escitalopram may be increased through inhibition of CYP2C19.
- *Fluconazole*—serotonin syndrome has been reported with this combination (also see ➔ *Pharmacodynamic*).
- *Lansoprazole*—plasma concentration of escitalopram may be increased through inhibition of CYP2C19.
- *Omeprazole*—plasma concentration of escitalopram may be increased through inhibition of CYP2C19.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of citalopram through inhibition of intestinal CYP3A4.

Pharmacodynamic

- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 251)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *TCAs*, *tapentadol*, *tramadol*, *trazodone*.
- Escitalopram is associated with a known risk of dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 251).

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.
- *Antidiabetics*—SSRIs may alter glycaemic control; risk of impaired awareness of hypoglycaemia.
- *Carbamazepine*—increased risk of hyponatraemia.
- *Cyproheptadine*—may inhibit the effects of serotonin reuptake inhibitors.
- *Diuretics*—increased risk of hyponatraemia.
- *Lithium*—may enhance the effect of SSRIs.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).
- *NSAIDs*—increased risk of GI bleeding (potentially worse with aspirin and naproxen).
- *SNRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

NB—the drops can be mixed with water, orange juice, or apple juice before taking.

Depression

- Initial dose: 10mg PO OD. The dose should be reviewed after 2–3 weeks and increased, if necessary, to a maximum of 20mg PO OD.

Panic

- Initial dose: 5mg PO OD. The dose can be increased after 7 days to 10mg PO OD. The dose can be further increased, if necessary, to a maximum of 20mg PO OD.

Generalized anxiety

- Initial dose: 10mg PO OD. Increase as necessary up to 20mg PO OD.

Dose adjustments

Elderly

- Initial dose is 5mg PO OD, increased to a maximum of 10mg PO OD.

Hepatic/renal impairment

- Patients with mild to moderate hepatic impairment, or those known to be poor CYP2C19 metabolizers, should have an initial dose of 5mg PO OD for the first 2 weeks of treatment. The dose can be increased to a maximum of 10mg PO OD if necessary. In severe hepatic impairment, the manufacturer recommends caution and extra careful dose titration. SSRIs can increase the risk for GI bleeding from varices.
- No dosage adjustment is necessary in mild or moderate renal impairment. The manufacturer advises caution in patients with severe renal impairment (CrCl <30mL/min).

Additional information

- Response in depression may be evident within the first week of treatment; generally, an effect is seen after at least in the second week of treatment but may take up to 4 weeks.
- Symptoms of anxiety or panic may worsen on initial therapy. This can be minimized by using lower starting doses. Maximum effectiveness is reached after about 3 months.
- If withdrawal symptoms emerge during discontinuation, increase the dose to prevent symptoms and then start to withdrawal more slowly.

Pharmacology

Escitalopram is the S-enantiomer of citalopram. It is a highly selective inhibitor of neuronal serotonin reuptake, with only very minimal effects on noradrenaline and dopamine neuronal reuptake. Escitalopram has no, or exceptionally low, affinity for opioid, serotonergic (5-$HT_{1–7}$), muscarinic ($AChm_{1–5}$), α-adrenergic ($\alpha_{1–2}$), β-adrenergic, dopamine ($D_{1–5}$), histamine ($H_{1–3}$), or benzodiazepine receptors. Escitalopram is metabolized primarily by CYP2C19 to active metabolites, but these are unlikely to contribute to the overall antidepressant effect. Escitalopram is eliminated by both the hepatic and renal routes, with the major part of a dose being eliminated as metabolites in the urine.

Reference

1. Aboukarr A, Giudice M. Interaction between monoamine oxidase B inhibitors and selective serotonin reuptake inhibitors. *Can J Hosp Pharm.* 2018;**71**(3):196–207.

Esomeprazole ♡

Nexium® (POM)

Tablet (gastro-resistant): 20mg (28); 40mg (28).
Granules (gastro-resistant): 10mg (28).
IV injection/infusion: 40mg.

Generic® (POM)

Tablet (gastro-resistant): 20mg (28); 40mg (28).
Capsule (gastro-resistant): 20mg (28); 40mg (28).
IV injection/infusion: 40mg.
NB—esomeprazole 20mg tablets can be sold OTC for short-term relief of reflux-like symptoms (e.g. heartburn) in adults aged over 18 years; maximum daily dose of 20mg PO for a maximum of 4 weeks.

Indications

- Treatment of gastric and duodenal ulcer.
- Treatment of reflux oesophagitis.
- Treatment and prophylaxis of NSAID-associated benign gastric and duodenal ulcers requiring continual therapy.
- Symptomatic gastro-oesophageal reflux disease.
- †Administration by CSCI.
- Eradication of *Helicobacter pylori* (*not discussed*).
- Zollinger–Ellison syndrome (*not discussed*).

Contraindications and cautions

- Increased gastric pH resulting from esomeprazole treatment may critically affect absorption of certain drugs (see ➲ *Drug interactions*, p. 257).
- Treatment with esomeprazole may lead to a slightly increased risk of developing GI infections (e.g. *Clostridium difficile*). Therefore, avoid unnecessary use or high doses.
- Rebound acid hypersecretion may occur on discontinuation if the patient has received >8 weeks' treatment.
- Esomeprazole is predominantly metabolized by CYP2C19, and by CYP3A4 to a lesser extent. Factors affecting CYP2C19 activity, such as phenotype (see Box 1.3) and drugs (see ➲ *Drug interactions*, p. 257), can alter response and adverse effects.
- Proton pump inhibitors (PPIs) are associated with a range of electrolyte disturbances such as hyponatraemia and hypomagnesaemia (and associated hypocalcaemia and hypokalaemia). Consider the PPI as the cause, should unexplainable symptoms be present (e.g. confusion, delirium, generalized weakness, nausea). The effect on Na^+ metabolism is unclear, possibly involving ADH. PPIs may reduce active magnesium (Mg^{2+}) absorption in the small intestine by affecting the function of a transient receptor protein channel. Poor metabolizer status may contribute to such adverse effects.
- There is a *conditional* risk of QT prolongation/TdP due to a propensity to cause significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia). Monitor electrolytes regularly in patients with

known QT interval prolongation or congenital long QT syndrome and in those taking drugs that prolong the QT interval (see ➔ *Drug interactions*).
- When used in high doses and over long durations (>1 year), PPIs may increase the risk of hip, wrist, and spine fracture, predominantly in the elderly or in the presence of other recognized risk factors. Consider the need for adequate vitamin D and calcium intake.
- Esomeprazole may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Common*: abdominal pain; constipation; diarrhoea; flatulence; fundic gland polyps (benign); headache; nausea; vomiting.
- *Uncommon*: dermatitis; dizziness; drowsiness; dry mouth; insomnia; increased liver enzymes; osteoporosis; paraesthesia; peripheral oedema; pruritus; raised liver enzymes; rash; urticaria; vertigo.
- *Rare*: agitation; alopecia; arthralgia; bronchospasm; confusion; depression; hepatitis with or without jaundice; hypersensitivity reactions (e.g. fever, angioedema); hyponatraemia; leucopenia; malaise; myalgia; photosensitivity; stomatitis; increased sweating; taste disturbance; thrombocytopenia; visual disturbances (e.g. blurred vision).
- *Very rare*: aggression; agranulocytosis; erythema multiforme; gynaecomastia; hallucinations; hepatic failure; interstitial nephritis; muscular weakness; pancytopenia; renal failure; Stevens–Johnson syndrome; toxic epidermal necrolysis.
- *Not known*: hypomagnesaemia (may correlate with hypocalcaemia and/or hypokalaemia).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Esomeprazole is metabolized by CYP2C19 (major) and CYP3A4 (minor); it is an inhibitor of CYP2C19. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Drugs with pH-dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced
  - *iron supplements*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g.

200mg per 30mg elemental iron) at the same time as the iron supplement to improve absorption
  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations
  - *metronidazole suspension*—esomeprazole may reduce/prevent the absorption of metronidazole.
- *Azole antifungals*—fluconazole may cause increased esomeprazole concentrations (CYP2C19 inhibition).
- *Citalopram*—plasma concentration of citalopram *may* be increased through inhibition of CYP2C19.
- *Clarithromycin*—inhibition of CYP3A4 metabolism can lead to increased esomeprazole concentrations.
- *Clopidogrel*—antiplatelet action may be reduced (the SmPC recommends avoiding combination).
- *Diazepam*—plasma concentration of diazepam *may* be increased through inhibition of CYP2C19.
- *Escitalopram*—plasma concentration of escitalopram *may* be increased through inhibition of CYP2C19.
- *Methotrexate*—esomeprazole may cause increase in concentrations of methotrexate; consider withholding esomeprazole.
- *Phenobarbital*—plasma concentration of phenobarbital *may* be increased through inhibition of CYP2C19.
- *Phenytoin*—plasma concentration of phenytoin *may* be increased through inhibition of CYP2C19.
- *Tacrolimus*—serum concentrations of tacrolimus may be increased by esomeprazole.
- *Voriconazole*—inhibition of CYP2C19 by esomeprazole may increase concentrations of voriconazole.
- *Warfarin*—possible increase in INR.
- The clinical significance of co-administration with CYP2C19 inducers or inhibitors (see ➔ *Inducers* and *Inhibitors* on the inside back cover) is unknown. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary.
- The clinical significance of co-administration with CYP3A4 inducers or inhibitors (see ➔ *Inducers* and *Inhibitors* on the inside back cover) is unknown. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary.
- The clinical significance of co-administration of other CYP2C19 substrates (see ➔ *Substrates* on the inside back cover) is unknown. Caution is advised if esomeprazole is co-administered with drugs that are predominantly metabolized by CYP2C19. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Pharmacodynamic

- Esomeprazole may cause prolongation of the QT interval due to a propensity to cause electrolyte disturbances. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*,

domperidone, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Corticosteroids*—concurrent use may increase the risk of osteoporosis and osteoporotic fractures.

Dose

Gastro-oesophageal reflux disease
- With oesophagitis, initial dose 40mg PO OD for 4 weeks. Continue for a further 4 weeks if not fully healed or symptoms persist.
- Alternatively, in patients unable to tolerate oral therapy, 40mg IV or IVI OD.
- Maintenance dose 20mg PO OD.
- In the absence of oesophagitis, initial dose 20mg PO OD for up to 4 weeks.
- Alternatively, in patients unable to tolerate oral therapy, 20mg IV or IVI OD.
- Maintenance dose 20mg PO OD PRN.

Treatment of NSAID-associated gastric ulcer
- Initial dose 20mg PO OD for 4–8 weeks.
- Alternatively, in patients unable to tolerate oral therapy, 20mg IV or IVI OD.

Prophylaxis of NSAID-associated peptic ulcer disease
- 20mg PO OD.
- Alternatively, in patients unable to tolerate oral therapy, 20mg IV or IVI OD.

†Administration by CSCI
- There are case reports of esomeprazole being administered via CSCI.[1] Concentrations of esomeprazole solution of between 0.4mg/mL and 0.8mg/mL can be administered by continuous IV infusion (CIVI), and these form the basis for CSCI administration. A dose of 20mg by CSCI has been administered in a volume of 33mL of NaCl.
- A dose of 40mg esomeprazole has been administered in 50mL of NaCl by short SUBCUT infusion over 30 minutes.[2]

Dose adjustments

Elderly
- Dose adjustments are not necessary in the elderly.

Hepatic/renal impairment
- In patients with mild to moderate liver impairment, no dose adjustments are necessary. For patients with severe liver impairment, the dose should not exceed 20mg OD.
- The manufacturer states that dose adjustments are not required in patients with renal impairment, although patients with severe renal impairment should be treated with caution due to limited experience.

Additional information

- The tablet can be dispersed in water to form a suspension of enteric-coated granules. The solution can be swallowed or administered via a feeding tube. The tablet dispersion, or granules for suspension, can also be administered via a nasogastric tube. Refer to the SmPC for specific details.
- IV injection should be administered over at least 3 minutes.
- IVI should be administered over a period of 10–30 minutes.

Pharmacology

Esomeprazole is the S-isomer of omeprazole. It is a PPI that suppresses gastric acid secretion in a dose-related manner by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. Esomeprazole is rapidly absorbed orally, with a bioavailability of 89% after repeated dosing. It is completely metabolized by the liver, with CYP2C19 being involved in the major metabolic pathway. CYP3A4 is also involved in the metabolism of esomeprazole, but to a lesser extent. The major metabolites of esomeprazole are inactive.

Reference

1. Hindmarsh J, Adelaja M, Abd Latif S, Lee M, Pickard J. Administering esomeprazole subcutaneously via a syringe driver in the palliative demographic: a case series. *J Clin Pharm Ther*. 2022;**47**(5):694–8.
2. Desmidt T, Constands T. Subcutaneous infusion of esomeprazole in elderly patients in palliative care: a report of two cases. *J Am Geriatr Soc*. 2009; **57**(9):1724–5.

Etoricoxib

Arcoxia® (POM)

Tablet: 30mg (28); 60mg (28); 90mg (28); 120mg (7; 28).

Generic (POM)

Tablet: 30mg (28); 60mg (28); 90mg (28); 120mg (7; 28).

Indications

- Pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.
- Acute gout.
- †Pain associated with cancer.[1,2]

Contraindications and cautions

- Etoricoxib is contraindicated for use in patients with:
  - active peptic ulceration or active GI bleeding
  - congestive heart failure—NYHA classes II–IV
  - established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease
  - hypersensitivity reactions (e.g. asthma, nasal polyps, rhinitis) to aspirin or other NSAIDs, including COX-2 inhibitors
  - hypertension persistently elevated above 140/90mmHg and which has not been adequately controlled
  - inflammatory bowel disease
  - severe hepatic dysfunction (serum albumin <25g/L or Child–Pugh score ≥10)
  - severe renal impairment (estimated renal CrCl <30mL/min).
- Risks of toxicity may increase with dose and duration of exposure. Use the minimum effective dose for the shortest duration necessary in order to reduce the risk of cardiac and GI events. Treatment should be reviewed *2 weeks* after initiation and the continued need for treatment should be regularly reassessed. In the absence of benefit, other options should be considered.
- Elderly patients are more at risk of developing adverse effects.
- Use with caution in the following circumstances:
  - concurrent use of oral anticoagulants, diuretics, corticosteroids, and other NSAIDs (see *Drug interactions*, p. 263)
  - congestive heart failure and/or left ventricular dysfunction
  - diabetes mellitus (risk factors for CV events)
  - hepatic impairment (see below)
  - hyperlipidaemia
  - hypertension (particularly uncontrolled)
  - prior history of GI disease
  - recovery from surgery
  - renal impairment
  - smoking (higher risk of CV and GI toxicity).
- Before initiating longer-term treatment, risk factors for CV disease should be considered (e.g. diabetes mellitus, hyperlipidaemia, hypertension, smoking).

- Hepatic insufficiency may occur with long-term treatment. Patients with pre-existing liver disease should be monitored. If persistently abnormal LFTs (three times the upper limit of normal) are detected, etoricoxib should be discontinued.
- Etoricoxib is associated with a greater risk of hypertension, compared to other NSAIDs or COX-2 inhibitors. Hypertension should be controlled before treatment with etoricoxib. Monitor BP and renal function in patients at risk of CV adverse effects during the first 2 weeks of initiation (or dose increase).
- Etoricoxib may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of etoricoxib. Patients appear to be at highest risk within the first month of treatment. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with etoricoxib must not be restarted.
- Consider co-prescription of misoprostol or a PPI if at high risk of NSAID-induced GI toxicity, e.g. long-term NSAID therapy, concurrent use of drugs that increase the risk of GI toxicity (see ➔ *Drug interactions*, p. 263).
- Refer to ➔ Chapter 2, *Selection of an NSAID,* p. 49 for further information about selecting an NSAID.
- Etoricoxib may cause dizziness, drowsiness, or vertigo. Patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: abdominal pain.
- *Common*: alveolar osteitis; arrhythmia; asthenia; bronchospasm; constipation; diarrhoea; dizziness; dyspepsia; ecchymosis; epigastric discomfort; flatulence; gastritis; headache; hypertension; increased liver enzymes; oesophagitis; nausea; oedema; palpitations; reflux; vomiting.
- *Uncommon*: abdominal distension; anaemia (usually associated with GI bleeding); angina; anxiety; appetite change (increase or decrease); atrial fibrillation; cerebrovascular accident; chest pain; congestive heart failure; cough; depression; drowsiness; dry mouth; dysgeusia; dyspnoea; erythema; epistaxis; facial oedema; flushing; gastroenteritis; gastroduodenal ulcer; GI perforation and bleeding; hallucinations; hyperkalaemia; hypersensitivity; hypertensive crisis; infection (e.g. conjunctivitis, gastroenteritis, upper respiratory infection, urinary tract infection); insomnia; irritable bowel syndrome; leucopenia; muscle cramp; myocardial infarction; pancreatitis; paraesthesia; pruritus; rash; renal failure; tachycardia; thrombocytopenia; tinnitus; transient ischaemic attack; urticaria; vasculitis; vertigo; visual disturbance (e.g. blurred vision); weight gain.
- *Rare*: angioedema; anaphylaxis; confusion; hepatitis; hyponatraemia; jaundice; restlessness; Stevens–Johnson syndrome; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized primarily by CYP3A4. *In vitro* data suggest CYP2D6, CYP2C9, CYP1A2, and CYP2C19 could also catalyse the metabolism of etoricoxib, but their quantitative effect *in vivo* is unclear. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of etoricoxib through inhibition of intestinal CYP3A4.
- Etoricoxib is an inhibitor of human sulfotransferase, SULT1E1 in particular. The clinical consequences are presently unclear.
- *Digoxin*—monitoring of serum digoxin is recommended.
- *Lithium*—etoricoxib may reduce lithium renal excretion.

Pharmacodynamic

- *Anticoagulants (oral)*—risk of increase in INR (in patients established on anticoagulants) during etoricoxib initiation or dose escalation.
- *Antihypertensives*—reduced hypotensive effect.
- *Antiplatelet drugs*—increased risk of GI toxicity (no effect on antiplatelet action).
- *Corticosteroids*—increased risk of GI toxicity.
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Digoxin*—NSAIDs may exacerbate cardiac failure.
- *Diuretics*—increased risk of acute renal insufficiency (potential dehydration and/or hypovolaemia).
- *SSRIs*—increased risk of GI bleeding.
- *Trimethoprim*—increased risk of hyperkalaemia.

Dose

Ensure gastroprotection (e.g. PPI) is prescribed for patients at risk of NSAID-induced GI toxicity.

Osteoarthritis

- 30mg PO OD, increased to 60mg PO OD as necessary.

Rheumatoid arthritis/ankylosing spondylitis

- 60mg PO OD, increased to 90mg PO OD as necessary. Once stabilized, downtitration to 60mg PO OD should be considered.

Acute gout

- 120mg PO OD for a usual maximum of 8 days.

+Pain associated with cancer

- Initial dose 60mg PO OD, increased as necessary to 120mg PO OD (NB—risk of serious events increases with dose and duration). If no benefit after *2 weeks*, discontinue treatment and review.

Dose adjustments

Elderly

- Usual adult doses recommended. Note that the elderly are particularly susceptible to adverse effects. Use the lowest effective dose and for the shortest duration possible.

Hepatic/renal impairment

- In patients with mild hepatic impairment (Child–Pugh score 5–6), 60mg PO OD should not be exceeded. In patients with moderate hepatic impairment (Child–Pugh score 7–9), 30mg PO OD should not be exceeded. Etoricoxib is contraindicated for use in patients with severe hepatic impairment, due to lack of clinical experience.
- Use of etoricoxib in patients with severe renal impairment is contraindicated. No dosage adjustment is necessary for patients with CrCl ≥30mL/min.

Additional information

- Etoricoxib tablets may be dispersed in water prior to administration.
- To increase the speed of onset, etoricoxib should be taken without food.

Pharmacology

Like traditional NSAIDs, the mechanism of action of etoricoxib is believed to be due to inhibition of prostaglandin synthesis. Unlike most NSAIDs, however, etoricoxib is a selective, non-competitive inhibitor of COX-2. It has no effect on platelet aggregation. Etoricoxib is well absorbed orally, with an absolute bioavailability of 100%. It is extensively metabolized, with CYP3A4 being the major CYP enzyme involved. Some of the metabolites are weakly active COX-2 inhibitors, whereas the rest have no appreciable action. Less than 1% of the total dose is excreted unchanged in the urine.

References

1. Derry S, Wiffen PJ, Moore RA, *et al*. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database Syst Rev*. 2017;**7**:CD012638.
2. Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. *Br J Anaesth*. 2019;**123**(2):e412–23.

Exemestane

Aromasin® (POM)
Tablet: 25mg (30; 90).

Generic (POM)
Tablet: 25mg (30).

Indications

- Adjuvant treatment of oestrogen receptor-positive early breast cancer in post-menopausal women following 2–3 years of tamoxifen therapy.
- Advanced breast cancer in post-menopausal women in whom anti-oestrogen therapy has failed.

Contraindications and cautions

- Not to be used in premenopausal women.
- Use with caution in patients with hepatic or renal impairment.
- May cause reduction in bone mineral density and an increased fracture rate. Women with osteoporosis or at risk of osteoporosis should have their bone mineral density formally assessed and treatment should be initiated in at-risk patients.
- Exemestane may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: abdominal pain; depression; dizziness; fatigue; headache; hot flushes; increased sweating; insomnia; leucopenia; increased liver enzymes; musculoskeletal pain; nausea.
- *Common*: alopecia; anorexia; asthenia; carpal tunnel syndrome; constipation; diarrhoea; dyspepsia; fracture; osteoporosis; paraesthesia; peripheral oedema; pruritus; rash; thrombocytopenia; urticaria; vomiting.
- *Uncommon*: hypersensitivity.
- *Rare*: acute generalized exanthematous pustulosis; drowsiness; hepatitis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized by CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- The effect of grapefruit juice on the absorption of exemestane is unknown.

Pharmacodynamic

- *Oestrogens*—may antagonize the effect of exemestane.

Dose

- 25mg PO OD, after food.

Dose adjustments

Elderly

- Dose adjustments are unnecessary.

Hepatic/renal impairment

- Although caution is advised, the SmPC does not recommend dose adjustments for patients with liver or renal impairment.

Additional information

- In patients with early breast cancer, treatment should continue until completion of 5 years of combined sequential adjuvant hormonal therapy (tamoxifen followed by exemestane), or earlier if tumour relapse occurs.
- In patients with advanced breast cancer, treatment should continue until tumour progression is evident.

Pharmacology

Exemestane is an irreversible steroidal aromatase inhibitor which does not possess any progestogenic, androgenic, or oestrogenic activity. It reduces oestrogen concentrations by blocking the action of aromatase in the adrenal glands.

Famotidine ♡

Generic (POM)
Tablet: 20mg (28); 40mg (28).

Unlicensed (POM)
Injection: 20mg/2mL (see ➔ *Additional information*, p. 269)

Indications

- Benign gastric ulcer.
- Duodenal ulcer.
- Prevention of duodenal ulcer recurrence.
- Symptomatic treatment of mild to moderate reflux oesophagitis.
- Zollinger–Ellison syndrome.
- [+]Prevention of NSAID-associated gastroduodenal ulcers.

Contraindications and cautions

- Use with caution in patients with renal impairment (see ➔ *Dose adjustments*, p. 269).
- If long-term treatment at high dosages, the SmPC recommends monitoring of blood counts and LFTs.
- The SmPC advises against abrupt withdrawal after long-term treatment.
- There is a *conditional* risk of QT prolongation/TdP (most likely to be associated with accumulation and renal impairment) with famotidine. Although not specifically mentioned in the SmPC, it is recommended that an assessment of the balance of risks and benefits is made before prescribing famotidine to patients:
  - at high risk of serious cardiac arrhythmia or QT prolongation (e.g. *avoid* combination with other drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 268)
  - with known CV disease or a family history of QT interval prolongation.
- Famotidine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: constipation; diarrhoea; dizziness; headache.
- *Uncommon*: abdominal discomfort; anorexia; dry mouth; dysgeusia; fatigue; flatulence; nausea; vomiting.
- *Rare*: elevated LFTs.
- *Very rare*: agitation; alopecia; anxiety; arthralgia; blood dyscrasias (agranulocytosis, leucopenia, neutropenia, pancytopenia, thrombocytopenia); chest tightness; confusion; convulsions (linked to renal impairment); depression; hallucinations; hepatitis; hypersensitivity reactions (anaphylaxis, bronchospasm); impotence; insomnia; interstitial pneumonia; jaundice; reduced libido; paraesthesia; QT prolongation; somnolence; Stevens–Johnson syndrome; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Famotidine is principally excreted via the kidneys as unchanged drug (25–60%). It is unlikely to be involved in cytochrome-related interactions.
- *Antacids*—concomitant use of antacids can reduce the absorption of famotidine; give famotidine 1–2 hours beforehand.
- Drugs with pH-dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced
  - *ferrous sulfate*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g. 100mg) at the same time as ferrous sulfate to improve absorption
  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations; give 2 hours before famotidine
  - *metronidazole suspension*—ranitidine may reduce/prevent the absorption of metronidazole.

Pharmacodynamic

- Famotidine has been associated rarely with dose-related prolongation of the QT interval, usually in patients with renal impairment. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*).
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).

Dose

Benign gastric or duodenal ulceration

- 40mg PO OD (evening) for 4–8 weeks.

Prevention of duodenal ulcer recurrence

- 20mg PO OD (evening).

Reflux oesophagitis

- 20mg to 40mg BD for up to 6–12 weeks.
- †Maintenance can be continued at 20mg PO BD.

†NSAID-associated ulceration

- 40mg PO BD.

Zollinger–Ellison syndrome

- Initial dose 20mg PO every 6 hours. Doses are then adjusted to individual response to a maximum of 800mg/day.

✢ *SUBCUT/CSCI*

- Famotidine has been given by SUBCUT injection and CSCI:
  - 20mg SUBCUT BD
  - 40 mg CSCI every 24 hours, using NaCl or WFI as the diluent. Note there are no compatibility data currently.

Dose adjustments

Elderly

- Usual adult doses can be used.

Hepatic/renal impairment

- Famotidine is principally excreted via the kidneys, so liver impairment is unlikely to have a significant impact.
- Dose adjustments are necessary in renal impairment. The SmPC recommends a dose reduction of 50% in patients with CrCl <10mL/min (or give the normal dose ALT DIE). Note this is different to the information that appeared in the previous SmPC (which stated a dose reduction was necessary in patients with CrCl <30mL/min).

Additional information

- The injection formulation is unavailable in the UK, but is available to import.

⊰ Pharmacology

Famotidine is a potent, selective, competitive, and fully reversible H_2 receptor antagonist. It significantly decreases basal and stimulated gastric acid and pepsin concentrations, in addition to the volume of gastric secretions. Nocturnal gastric acid secretion is significantly inhibited for up to 12 hours with a dose of 40mg PO ON. Renal excretion of unchanged drug accounts for 25–60% of a dose; hepatic metabolism produces the inactive sulfoxide metabolite. Moderate to severe renal impairment significantly reduces the clearance of famotidine.

Fentanyl (transdermal/parenteral)

Transdermal

Durogesic DTrans® (CD2 POM)

Patch (matrix): 12 micrograms/hr (5); 25 micrograms/hr (5); 50 micrograms/hr (5); 75 micrograms/hr (5); 100 micrograms/hr (5).

Generic (CD2 POM)

Patch (matrix): 12 micrograms/hr (5); 25 micrograms/hr (5); 37.5 micrograms/hr (5) (*Mezolar®*); 50 micrograms/hr (5); 75 micrograms/hr (5); 100 micrograms/hr (5).

Brands include: Fencino®, Matrifen®, Mezolar®, Osmanil®, and Victanyl®.

NB—there have been reports of crystals appearing in Fencino® transdermal patches. The SmPC states these patches can still be used, provided crystallization does not affect >10% of the patch surface area. Consult with a pharmacist if there are any concerns.

Generic (CD2 POM)

Patch (reservoir): *Fentalis® Reservoir* (*discontinued in July 2021—stocks should no longer be available*).

Parenteral

Sublimaze® (CD2 POM)

Injection: 100 micrograms/2mL (10); 500 micrograms/10mL (5).

Generic (CD2 POM)

Injection: 100 micrograms/2mL (10); 500 micrograms/10mL (10).

Solution for infusion: 2.5mg/50mL (1).

Indications

- Severe chronic pain (*transdermal*).
- †Treatment of severe pain via SUBCUT administration (*parenteral*).

Contraindications and cautions

Large numbers of patient safety incidents involving transdermal fentanyl patches have been reported to the NRLS. The Care Quality Commission/NHS England recommendations[1] are summarized below.

1. Transdermal fentanyl patches should be restricted to patients who are already receiving regular doses of opioids.
   i. Do not use for acute pain.
   ii. Do not use in opioid-naïve patients (contraindicated by the CHM).
2. Before using a transdermal fentanyl patch, calculate the total daily dose of all opioid analgesics that the patient has received previously. This is usually in morphine equivalence. Use locally or nationally approved dose conversion charts to do this (also see ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56).

3. Determine a new dose of analgesia to be delivered by transdermal fentanyl patch in morphine equivalents. Ensure the total daily dose is not increased in steps of >50% of the previous daily dose. Note that more than one transdermal fentanyl patch may have to be used.
4. Patches may be difficult to locate, given their size and colour. Note that some products (e.g. *Durogesic DTrans®*) are now supplied with a coloured border to aid visualization. Formally record the anatomical position of currently applied patches, so that this information is readily available to inform future decisions and actions.
5. Prescribe transdermal fentanyl patches by brand to avoid confusing patients or carers.
6. Patients may exhibit symptoms of opioid withdrawal when a transdermal fentanyl patch has been omitted. Ensure that opioid treatment is reinstated, at lower doses if appropriate.
7. Approximately 40% of the initial amount of fentanyl remains in the transdermal patch after 72 hours—ensure adequate disposal is discussed with the patient; patches must be removed and replaced, in accordance with the specific product SmPC instructions or, where applicable, local guidelines.

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care. There may, however, be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation). Nonetheless, contraindications and cautions are described below.
- The SmPCs for fentanyl products contraindicate concurrent administration with MAOIs or within 2 weeks of their discontinuation (risk of serotonin toxicity—see Chapter 1, *Serotonin toxicity*, p. 29). If concomitant use is unavoidable (e.g. *linezolid*), ensure there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- *Fencino®* is contraindicated for use in patients with soya and/or peanut allergy.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see *Drug interactions*, p. 273). Of the opioids, *morphine* is believed to carry the lowest risk. Treatment must be reviewed urgently if symptoms develop, fentanyl should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[2] The SmPC warns that concurrent use of fentanyl and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the

lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.

- Use with caution in patients with:
  - bradyarrhythmias (fentanyl may induce bradycardia)
  - brain tumours (risk of raised intracranial pressure)
  - cachexia (absorption impaired, with serum concentrations reduced by 33–50%)
  - concurrent use of CNS depressants and/or CYP3A4 inducers or inhibitors (see ➔ *Drug interactions*, p. 273)
  - concurrent use of serotonergic drugs (see ➔ *Drug interactions*, p. 273)
  - hypertension (fentanyl can cause hypertension)
  - hypotension (fentanyl may cause hypotension)
  - hypovolaemia (increased risk of hypotension)
  - hepatic impairment (empirical dose adjustment may be necessary—see ➔ *Dose adjustments*, p. 276)
  - myasthenia gravis (non-epileptic (myo)clonic reactions can occur)
  - pyrexia (increased fentanyl delivery rate)
  - severe respiratory disease (respiratory effects of opioids are more pronounced during sleep).
- Fentanyl may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

Parenteral

- As above, although there are no specific contraindications if being used for end-of-life care via CSCI.

Transdermal

- Transdermal fentanyl should not be used in opioid-naïve patients. Such patients should be titrated with low doses of short-acting opioids initially. If transdermal fentanyl is to be used in opioid-naïve patients, this should only be under specialist supervision since such use has been associated with rare cases of significant respiratory depression.
- Patients should be advised to avoid exposing the patch application site to direct heat sources, such as direct sunlight, hot water bottles, electric

blankets, heat lamps, saunas, or baths, because of the risk of increased fentanyl absorption. A 3°C increase in body temperature elevates the peak fentanyl plasma concentration by 25%.
- Patients who experience serious adverse events should have the patches removed immediately and should be monitored for up to 24 hours after patch removal.
- If treatment with transdermal fentanyl is to be discontinued, the patient must be switched to an alternative (e.g. morphine, oxycodone) to enable dose reduction and avoidance of opioid withdrawal symptoms (see ➔ *Additional information*, p. 276).

Adverse effects

Strong opioids tend to cause similar adverse effects, albeit to varying degrees. The frequency of adverse effects varies, depending on formulation. Each product has its own list and frequency of adverse effects. Some are shown below, but readers should refer to the individual SmPC for further details.
- *Very common*: constipation; dizziness; drowsiness; headache; muscle rigidity—may also involve thoracic muscles (parenteral only); nausea; vomiting.
- *Common*: abdominal pain; anorexia; anxiety; asthenia; confusional state; depression; diarrhoea; dry mouth; dyspepsia; dyspnoea; erythema; fatigue; hallucinations; hyperhidrosis; hypersensitivity; hypertension (possibly due to unexplained alterations in sympathetic activity); insomnia; muscle spasm; oedema; palpitations; paraesthesia; pruritus; rash; tachycardia; tremor; urinary retention; vertigo.
- *Uncommon*: agitation; amnesia; application site reaction; bradycardia; convulsion; cyanosis; disorientation; euphoria; hypotension; ileus; muscle twitching; respiratory depression; sexual dysfunction (e.g. erectile dysfunction); visual disturbances (e.g. blurred vision).
- *Unknown*: hyperalgesia; tolerance (to analgesic effect).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Fentanyl is a major substrate of CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Caution should be used if CYP3A4 inhibitors (see ➔ *Inhibitors* on the inside back cover) are initiated in patients already prescribed transdermal fentanyl patches due to the increased risk of extended therapeutic and adverse effects.
- Examples of potential interactions include:
  - *aprepitant*—with acute treatment, aprepitant can enhance the effect of fentanyl (moderate CYP3A4 inhibition—greater effect on orally

administered drugs); within 3–5 days of completing a 3-day course of aprepitant, the effect of fentanyl may be reduced (mild CYP3A4 induction)
- *carbamazepine*—the patient may need higher doses of fentanyl if carbamazepine is introduced to treatment
- *clarithromycin*—may inhibit the metabolism of fentanyl; dose reduction may be necessary
- *dexamethasone*—high dose (e.g. 12mg to 16mg PO OD) may reduce the efficacy of fentanyl
- *erythromycin*—may enhance the effect of fentanyl; dose reduction may be necessary
- *fluconazole*—may inhibit the metabolism of fentanyl (although more likely to occur when fluconazole doses are >200mg daily)
- *midazolam*—effect may be enhanced by fentanyl (competitive inhibition of metabolism)
- *phenobarbital*—may reduce the efficacy of fentanyl
- *phenytoin*—may reduce the efficacy of fentanyl
- *rifampicin*—can reduce the efficacy of fentanyl.

Pharmacodynamic
- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 270)
  - *serotonergic drugs*—e.g. *mirtazapine*, *SNRIs*, *SSRIs*, *tapentadol*, *TCAs*, *tramadol*, *and trazodone*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 270.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing effect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and concurrent transdermal fentanyl use is not recommended; however, an empirical fentanyl dose reduction of 25–50% at least 12 hours *before* starting ketamine is suggested (additional opioid requirements can be treated using PRN analgesia).
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOIs*—risk of severe and unpredictable interactions with MAOIs, involving the potentiation of opioid or serotonergic effects
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 270.

Dose

Transdermal
- Patches should be worn continuously for 72 hours. Occasionally, certain patients may experience reduced efficacy in the period 48–72 hours after application. Such patients should replace the patch after 48 hours.

- The SmPC states the same site should be avoided for at least 'several' days (e.g. 3–7 days).
- Initial dosage of fentanyl is based upon previous opioid requirements. Refer to ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences. The SmPC's recommended equianalgesic ratio for PO morphine:transdermal fentanyl depends on the patient's situation and varies from 150:1 to 100:1. Refer to Tables 3.4 and 3.5.
- Patches should be applied firmly for approximately 30 seconds to ensure good adhesion. To aid adhesion, surgical tape can be applied around the edges of the patch; others suggest the use of an adhesive film dressing such as Tegaderm®.

Table 3.4 SmPC recommended starting dose based upon daily PO morphine dose *(for patients who have a need for opioid rotation or for clinically less stable patients, the conversion ratio of oral morphine to transdermal fentanyl is approximately equal to 150:1)*

PO morphine (mg/day)	Transdermal fentanyl (micrograms/hr)
<90	12
90–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300*

* The SmPC recommends that for dose requirements of >300 micrograms/hr, an alternative or additional method of analgesia should be used.

Parenteral

- The initial dose of fentanyl depends upon the patient's previous opioid requirements. See ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences.
- ✣ Initial dose in opioid-naïve patients is 12.5 micrograms to 25 micrograms 4-hourly SUBCUT PRN. Alternatively, 50 micrograms to 100 micrograms via CSCI over 24 hours and increase as necessary.

Table 3.5 SmPC recommended starting dose based upon daily PO morphine dose *(for patients on stable and well-tolerated opioid therapy, the conversion ratio of PO morphine to transdermal fentanyl is approximately equal to 100:1)*

PO morphine (mg/day)	Transdermal fentanyl (micrograms/hr)
≤44	12
45–89	25
90–149	50
150–209	75
210–269	100
270–329	125
330–389	150
390–449	175
450–509	200
510–569	225
570–629	250
630–689	275
690–749	300*

* The SmPC recommends that for dose requirements of >300 micrograms/hr, an alternative or additional method of analgesia should be used.

- Fentanyl via CSCI has been advocated for use in patients with severe renal and/or hepatic impairment. Given the volume constraints of the most commonly used infusion devices (typically 23mL for a 24-hour infusion), higher opioid requirements (e.g. >600 micrograms/day; approximately equivalent to 30mg/day SUBCUT morphine) will necessitate a switch to alfentanil.

Dose adjustments

Elderly

- No specific guidance available. Dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance is available, but dose adjustments and close monitoring are advisable in patients with severe liver impairment.
- Although the main route of elimination of fentanyl is hepatic metabolism, dose requirements should be individually titrated for patients with renal impairment (e.g. BUN >20mmol/L)—see *Pharmacology*, p. 279.

Additional information

- Opioid withdrawal symptoms (e.g. nausea, vomiting, diarrhoea, sweating, shivering) can occur in patients after switching from previously

prescribed opioids to a transdermal fentanyl patch. This is because a high percentage of the fentanyl dose partitions into the CNS, creating a withdrawal situation in the periphery. Rescue doses of morphine or oxycodone can be administered to treat these symptoms if warranted.
- If other analgesic measures are introduced—pharmacological or other alternatives, e.g. radiotherapy—the dose of fentanyl may need to be reduced.

Transdermal
- The SmPC advises that it may take up to 6 days for the patient to reach equilibrium on the new dose level. Evaluation of the analgesic effect should therefore not be made until the patch has been worn for at least 6 days (to allow for the gradual increase in plasma fentanyl concentration).
- In practice, assessment of response is usually made within 48–72 hours of patch application, particularly as steady-state plasma concentrations of fentanyl are generally achieved in 36–48 hours. If necessary, the dose should be adjusted at 72-hour intervals in steps of 12 to 25 micrograms/hr.
- During the first 72 hours following the initial patch application, PRN doses of rescue analgesia should be used to ameliorate potential withdrawal symptoms.
- The following is a guide on how to *initiate the patch* in relation to previous opioid therapy:
  - *standard-release* hydromorphone/morphine/oxycodone—give regular 4-hourly doses for the **first 12 hours** after applying the patch
  - *12-hourly* modified-release hydromorphone/morphine/oxycodone—give the final oral dose at the **same time** as applying the patch
  - *24-hourly* modified-release morphine/oxycodone—apply the patch **12 hours after** the final oral dose
  - CSCI—continue the syringe driver for the **first 12 hours** after applying the patch (consider continuing for **18 hours** in the case of switching from CSCI **alfentanil**).
- When converting from hydromorphone, morphine, or oxycodone to fentanyl, the dose(s) of any laxative(s) should be reduced (e.g. halved) and subsequently adjusted according to need.
- High quantities of fentanyl remain in the transdermal patches after a 72-hour period. Used transdermal patches should be folded, with the adhesive surfaces inwards, covering the release membrane.
- If a CSCI is needed, treatment should continue with the patch and additional analgesic requirements should be managed with suitable doses of rescue medication. Refer to ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences.
- Ensure that patients and caregivers are aware of the signs and symptoms of fentanyl overdose, i.e. sedation, confusion, feeling faint, dizzy, or confused. Patients and caregivers should be advised to seek medical attention immediately if overdose is suspected.
- Fentanyl patches should be removed prior to an MRI scan, due to the risk of heating. A new patch should be applied to a new site post-scan.

- The following is a suggestion on how to *switch* transdermal fentanyl to a *PO opioid formulation*. Note that serum fentanyl levels fall to 50% approximately 20 hours after patch removal and serum fentanyl levels may be reduced by 33–50% in cachectic patients (thereby affecting subsequent equianalgesia calculations):
  - *Standard-release* PO hydromorphone/morphine/oxycodone:
    - ensure usual PRN doses remain prescribed
    - remove the patch
    - determine the equianalgesic dose.
    - after a period of at least **12 hours**:
      - commence *regular* 4-hourly *standard-release* PO opioid at **50%** of the calculated equianalgesic dose
      - ensure the same dose of the *standard-release* PO opioid is prescribed for PRN use
      - *NB—the patient may have been using the same standard-release PO opioid for PRN use at different doses while prescribed transdermal fentanyl.*
      - review regular and PRN doses of the new opioid daily for the next **24 hours** after stopping transdermal fentanyl and consider switching to an oral modified-release opioid formulation at the earliest opportunity.
  - *12 hourly* modified-release PO hydromorphone/morphine/oxycodone:
    - ensure usual PRN doses remain prescribed
    - remove the patch
    - determine the equianalgesic dose.
    - after a period of at least **12 hours**:
      - commence the*12 hourly* modified-release PO opioid at **50%** of the calculated equianalgesic dose
      - ensure an appropriate dose of the *standard-release* PO opioid is prescribed for PRN use, based on the dose of the *12 hourly* modified-release PO opioid
      - *NB—the patient may have been using the same standard-release PO opioid for PRN use at different doses while prescribed transdermal fentanyl.*
      - review both regular and PRN doses of the new opioid **24 hours** after stopping transdermal fentanyl with a view to increase the PO opioid to **100%** of the calculated equianalgesic dose.
  - *24 hourly* modified-release PO morphine/oxycodone—avoid until a stable oral dose has been determined.

Parenteral

- After administration via CSCI, there is a degree of variability in both dosage and plasma concentrations of fentanyl, necessitating the need for careful dosage individualization and titration based on clinical response.
- Fentanyl is reportedly *chemically and physically* compatible under stated conditions with midazolam and ondansetron. Under stated conditions, fentanyl is reportedly *physically* compatible with dexamethasone, haloperidol, hyoscine hydrobromide, ketamine, ketorolac, levomepromazine, metoclopramide, and phenobarbital.[3]

Pharmacology

Fentanyl is a synthetic opioid, chemically related to pethidine, with an action primarily at the μ-receptor. It is believed to have a weak serotonin reuptake inhibitory effect (high doses) and act as a 5-HT_{1A} agonist. The main route of elimination is hepatic metabolism via CYP3A4 to inactive compounds, which are mainly excreted in the urine. The metabolites of fentanyl are non-toxic and inactive. Less than 10% of a dose is excreted unchanged in the urine. Fentanyl is a suitable opioid to use in patients with renal failure, although empirical dose adjustments will be necessary since hepatic metabolism of drugs with high hepatic extraction ratios is inhibited by uraemia, while factors affecting fentanyl distribution, such as binding to albumin and α_1-acid glycoproteins, can be highly variable. BUN above 20mmol/L is associated with significant changes in fentanyl clearance.[4]

References

1. Care Quality Commission and NHS England. Safer use of controlled drugs—preventing harms from fentanyl and buprenorphine transdermal patches. 2013. Available from: http://webarchive.nationalarchives.gov.uk/20161108035818/https:/www.cqc.org.uk/sites/default/files/documents/safer_controlled_drugs_guidance_for_the_web_fentanyl_and_buprenorphine_transdermal_patches_updated_v3.0.pdf. Accessed 6 August 2020.
2. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
3. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.
4. Koehntop DE, Rodman JH. Fentanyl pharmacokinetics in patients undergoing renal transplantation. *Pharmacotherapy*. 1997;**17**(4):746–52.

Fentanyl (transmucosal) ⚠

Oral transmucosal and nasal formulations are not identical and changing from one product to another will require a new dose titration. Therefore, it is recommended that patients should remain on the same product once treatment has been stabilized. Inclusion of the brand name on the prescription is suggested.

Abstral® (CD2 POM)
Sublingual tablet: 100 micrograms (10; 30); 200 micrograms (10; 30); 300 micrograms (10; 30); 400 micrograms (10; 30); 600 micrograms (30); 800 micrograms (30).
Actiq® (CD2 POM)
Lozenge: 200 micrograms (3; 30); 400 micrograms (3; 30); 600 micrograms (3; 30); 800 micrograms (3; 30); 1200 micrograms (3; 30); 1600 micrograms (3; 30).
Effentora® (CD2 POM)
Buccal tablet: 100 micrograms (4; 28); 200 micrograms (4; 28); 400 micrograms (4;28); 600 micrograms (4;28); 800 micrograms (4; 28).
Instanyl® (CD2 POM)
Nasal spray: 50 micrograms per spray (6 doses); 100 micrograms per spray (6 doses); 200 micrograms per spray (6 doses).
PecFent® (CD2 POM)
Nasal spray: 100 micrograms per spray (8 doses per bottle; 32 doses—4 × 8 doses per bottle); 400 micrograms per spray (8 doses per bottle; 32 doses—4 × 8 doses per bottle).
Generic (CD2 POM)
Lozenge: 200 micrograms (3); 400 micrograms (3); 600 micrograms (3); 800 micrograms (3); 1200 micrograms (3); 1600 micrograms (3).

Indications

- Breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Refer to ➔ Chapter 2, *Breakthrough cancer pain*, p. 54 for additional guidance.

Contraindications and cautions

- This section describes issues specific to transmucosal products. Also refer to ➔ *Fentanyl (transdermal/parenteral)*, p. 270 for additional relevant information.
- Contraindicated for use in:
  - opioid-naïve patients (patients must take at least 60mg/24 hours of oral morphine, or equivalent).
- NB—under specialist use, these products may be used in patients receiving <60mg/24 hours or oral morphine, or equivalent:[+]
  - previous facial radiotherapy (*Instanyl®*)
  - recurrent episodes of epistaxis (*Instanyl®*)
  - severe respiratory disease
  - treatment of acute pain other than breakthrough pain.
- The SmPCs for fentanyl products contraindicate concurrent administration with MAOIs or within 2 weeks of their discontinuation

(risk of serotonin toxicity—see ➔ Chapter 1, *Serotonin toxicity*, p. 29). If concomitant use is unavoidable (e.g. *linezolid*), ensure there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.

- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 282). Of the opioids, *morphine* is believed to carry the lowest risk. Treatment must be reviewed urgently if symptoms develop, fentanyl should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of fentanyl and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- The patient's background analgesia must be stabilized before use (otherwise the patient does not have breakthrough pain).
- Avoid concomitant use of a nasal vasoconstrictor (e.g. oxymetazoline) with *Instanyl*® and *PecFent*® (see ➔ *Drug interactions*, p. 282).
- Avoid concomitant use of other nasally administered medicinal products (effect on *Instanyl*® or *PecFent*® unknown).
- Use with caution in the following:
  - concurrent use of CYP3A4 inhibitors (see ➔ *Drug interactions*, p. 282)
  - diabetic patients (*Actiq*® lozenges contain 1.89g glucose per dose)
  - elderly (see ➔ *Dose adjustments*, p. 287)
  - head injury and/or raised intracranial pressure
  - hepatic impairment
  - oral lesions (absorption of fentanyl may be affected from oral formulations).
- An alternative method of treatment should be used if the patient experiences recurrent episodes of epistaxis or nasal discomfort (*Instanyl*® or *PecFent*®).
- Ensure good oral hygiene in order to prevent damage to teeth (*Actiq*®).
- *Effentora*® 100-microgram tablets contain 8mg of sodium (0.3mmol); the 200, 400, 600, and 800-microgram tablets each contain 16mg of sodium (0.6mmol).
- Fentanyl may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

- Strong opioids tend to cause similar adverse effects, albeit to varying degrees.
- Each product has its own list and frequency of adverse effects. Some are shown below, but refer to the manufacturer's SmPC for further details.
- Key: (a) = *Abstral*®; (b) = *Actiq*®; (c) = *Effentora*®; (d) = *Instanyl*®; (e) = *PecFent*®.
- *Very common*: abdominal pain[(b)]; application site reactions[(c)]; asthenia[(b)]; constipation[(b)]; drowsiness[(b)]; dizziness[(b,c)]; dyspnoea[(b)]; headache[(b,c)]; nausea[(a,b,c)]; vomiting[(b,c)].
- *Common*: abdominal pain[(c)]; anorexia[(b,c)]; anxiety[(b,c)]; application site reactions[(b)]; asthenia[(b,c)]; confusion[(b,c)]; constipation[(a,c,e)]; depression[(b,c)]; diarrhoea[(c)]; disorientation[(e)]; dizziness[(a,d,e)]; drowsiness[(a,c,d,e)]; dry mouth[(a,b,c)]; dysgeusia[(b,c,e)]; dyspepsia[(b,c)]; dyspnoea[(a,c)]; dyspepsia[(b,c)]; epistaxis[(e)]; fatigue[(a,c)]; flushing[(d)]; hallucinations[(b)]; headache[(a,d,e)]; hypertension[(c)]; hypotension[(c)]; insomnia[(c)]; migraine[(c)]; myoclonus[(b)]; nausea[(d,e)]; oedema[(c)]; oral candidosis[(c)]; pruritus[(b,c,e)]; rash[(c)]; rhinorrhoea[(e)]; stomatitis[(a,b,c)]; sweating[(a,b,c,d)]; tachycardia[(c)]; toothache[(c)]; tremor[(c)]; visual disturbances (e.g. blurred vision)[(b)]; vomiting[(a,d,e)].

Drug interactions

Pharmacokinetic

- As for fentanyl (see ➔ *Fentanyl (transdermal/parenteral)*, p. 270.
- Fentanyl should be used with caution if CYP3A4 inhibitors are co-prescribed due to the increased risk of extended therapeutic effects and adverse effects. Alterations in intestinal CYP3A4 activity (induction or inhibition) appear to have little influence on *transmucosal* fentanyl absorption or onset of effect. Nonetheless, since a significant proportion (approximately 75%) is swallowed and its systemic clearance may be decreased by CYP3A4 inhibitors, caution is required with co-administration.

Pharmacodynamic

- As for fentanyl (see ➔ *Fentanyl (transdermal/parenteral)*, p. 270.
- *Nasal vasoconstrictors*—can reduce effect of *Instanyl*® and *PecFent*®.

Dose

Transmucosal

Products are licensed for use in patients taking at least 60mg oral morphine per day or equivalent (see ➔ Chapter 2, Equianalgesia and opioid switch, p. 56 for information regarding opioid dose equivalences) for a week or longer. The effective dose of transmucosal formulations for breakthrough pain is not predictable from the daily maintenance dose of opioid and titration to an effective dose is necessary.

Abstral®

- No more than four sublingual tablets should be used for a single episode of breakthrough pain.

- During titration, if adequate analgesia is not obtained within 15–30 minutes of using the first sublingual tablet, a second tablet, as shown in Table 3.6, may be used. Should this be necessary, an increase in dose to the next highest tablet strength should be considered for the next episode of breakthrough pain.

Table 3.6 Titration schedule for Abstral®

BTcP episode	Dose of first *Abstral*® tablet per episode of breakthrough pain (micrograms)	Dose of additional *Abstral*® tablet to be taken 15–30 minutes after first tablet, if required (micrograms)
1st	100	100
2nd	200	100
3rd	300	100
4th	400	200
5th	600	200
6th	800	–

- Doses above 800 micrograms have not been evaluated.
- Maintain the patient on the dose established during titration. This may be >1 tablet per breakthrough pain incident.
- Allow at least 2 hours before treating another episode of breakthrough pain.
- If >4 episodes of breakthrough pain occur in a day for >4 consecutive days, review background analgesia and consider re-evaluating the dosing schedule.
- May discontinue abruptly if no longer required and the patient continues to receive chronic opioid treatment.

Actiq®

- During titration, if adequate analgesia is not obtained within 15 minutes of completing consumption of the first lozenge (i.e. 30 minutes after starting the first lozenge), a second lozenge of the same strength may be used. Refer to Table 3.7 for the titration schedule. Should this be necessary, an increase in dose to the next highest strength should be considered for the next episode of breakthrough pain. At 1600 micrograms, a second dose is only likely to be required by a minority of patients.
- If signs of excessive opioid effects appear before the lozenge is fully consumed, it should be immediately removed and the dose should be reviewed.
- No more than two lozenges should be used to treat a single episode of breakthrough pain.

Table 3.7 Titration schedule for Actiq®

BTcP episode	Dose of first *Actiq*® lozenge per episode of breakthrough pain (micrograms)	Dose of additional *Actiq*® lozenge to be taken 30 minutes after starting the first lozenge, if required (micrograms)
1st	200	200
2nd	400	400
3rd	600	600
4th	800	800
5th	1200	1200
6th	1600	1600

- The manufacturer does not specify a time limit before a second episode of breakthrough pain can be treated. Based on other products, allow at least 2–4 hours before treating another episode.
- Maintain the patient on the dose established during titration.
- *Actiq*® is for use in patients who typically experience no more than *four* episodes of breakthrough pain per day. If >4 episodes of breakthrough pain occur in a day for >4 consecutive days, review background analgesia and consider re-evaluating the dosing schedule.
- May discontinue abruptly if no longer required and the patient continues to receive chronic opioid treatment.

Effentora®

- During titration, if adequate analgesia is not obtained within 30 minutes of using the first buccal tablet, a second dose, as described in Table 3.8, can be used.

Table 3.8 Titration schedule for Effentora®

BTcP episode	Dose of first *Effentora*® buccal tablet per episode of breakthrough pain (micrograms)	Dose of additional *Effentora*® buccal tablet to be taken 30 minutes after starting first tablet, if required (micrograms)
1st	100	100
2nd	200 (use 2 × 100)	200 (use 1 × 200)
3rd	400 (use 2 × 200)	200 (use 1 × 200)
4th	600 (use 3 × 200)	200 (use 1 × 200)
5th	800 (use 4 × 200)	–

- No more than two tablets should be used to treat any individual breakthrough pain episode, *except* during titration, as described in Table 3.8.
- Patients should wait at least 4 hours before treating another episode of breakthrough pain.
- Doses above 800 micrograms have not been evaluated.
- If >4 episodes of breakthrough pain occur in a day for >4 consecutive days, review background analgesia and consider re-evaluating the dosing schedule.
- May discontinue abruptly if no longer required and the patient continues to receive chronic opioid treatment.

Instanyl®

- During titration, if adequate analgesia is not obtained after 10 minutes, an additional dose of the same strength can be administered *in the other nostril*.
- No more than two doses should be used to treat any individual breakthrough pain episode.
- Patients should wait at least 4 hours before treating another breakthrough pain episode with *Instanyl®* during both titration and maintenance therapy.
- Refer to Table 3.9 for the titration schedule.
- *Instanyl®* is licensed to be given for *four* episodes of breakthrough pain per day. If >4 episodes of breakthrough pain occur in a day for >4 consecutive days, or episodes of breakthrough pain occur <4 hours apart, review background analgesia and consider re-evaluating the dosing schedule.
- May discontinue abruptly if no longer required and the patient continues to receive chronic opioid treatment.

Table 3.9 Titration schedule for Instanyl®

BTcP episode	Dose of first *Instanyl®* nasal spray per episode of breakthrough pain (micrograms)	Dose of additional *Instanyl®* nasal spray to be used 10 minutes after first dose, if required (micrograms) *in the other nostril*
1st	50	50
2nd	100	100
3rd	200	200
4th	400	–

PecFent®

- Titration with *PecFent®* differs from the other products in that the effective dose is defined as the dose that successfully treats *two consecutive episodes of breakthrough pain*. During titration, an additional dose is not indicated.

Table 3.10 Titration schedule for PecFent®

BTcP episode	Dose of first *PecFent*® nasal spray per episode of breakthrough pain (micrograms)	Notes
1	100	If effective, *go to 2a* and continue with *100 micrograms* to treat the next episode of breakthrough pain. If ineffective, then for the next breakthrough pain episode, *go to 2b*.
2a	100	If effective, stop titration and continue with *100 micrograms*. If ineffective, then at the next breakthrough pain episode, *go to 3a*.
2b	200 (1 × 100 both nostrils)	If effective, *go to 3a* and continue with *200 micrograms* to treat the next episode of breakthrough pain. If ineffective, then for the next breakthrough pain episode, *go to 3b*.
3a	200 (1 × 100 both nostrils)	If effective, stop titration and continue with *200 micrograms*. If ineffective, then at the next breakthrough pain episode, *go to 4a*.
3b	400	If effective, *go to 4a* and continue with *400 micrograms* to treat the next episode of breakthrough pain. If ineffective, then at the next breakthrough pain episode, *go to 4b*.
4a	400	If effective, stop titration and continue with *400 micrograms*. If ineffective, then at the next breakthrough pain episode, *go to 5*.
4b	800 (1 × 400 both nostrils)	If effective, *go to 5* and continue with *800 micrograms* to treat the next breakthrough pain episode. If ineffective, contact a doctor for advice.
5	800 (1 × 400 both nostrils)	If effective, stop titration and continue with *800 micrograms*. If ineffective, contact a doctor for advice.

- No more than two doses (one spray in each nostril) should be used to treat any individual breakthrough pain episode.
- Patients should wait at least 4 hours before treating another breakthrough pain episode with *PecFent*® during both titration and maintenance therapy.
- Refer to Table 3.10 for the titration schedule.

- *PecFent*® is licensed to be given for *four* episodes of breakthrough pain per day. If >4 episodes of breakthrough pain occur in a day for >4 consecutive days, or episodes of breakthrough pain occur <4 hours apart, review background analgesia and consider re-evaluating the dosing schedule.
- May discontinue abruptly if no longer required and the patient continues to receive chronic opioid treatment.

Dose adjustments

Elderly

- No specific guidance available. Dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance available. Dose requirements should be individually titrated.

Additional information

- *Abstral*® sublingual tablets should be administered directly under the tongue and at the deepest part. The patient must not swallow, suck, or chew the tablet, nor should the patient eat or drink anything until the tablet has completely dissolved (happens within <1 minute). Water may be used to moisten the buccal mucosa in patients with a dry mouth.
- *Actiq*® lozenges should be rubbed against the cheek or sucked, but not chewed. Water may be used to moisten the buccal mucosa in patients with a dry mouth. The lozenge should be consumed within 15 minutes.
- *Effentora*® buccal tablets should be placed in the upper portion of the buccal cavity (above an upper rear molar between the cheek and gum). The tablet should not be sucked, chewed, or swallowed, nor should the patient eat or drink anything while the tablet is in the mouth. The tablet usually disintegrates within 14–25 minutes; after 30 minutes, the mouth can be rinsed to remove the remnants. Water may be used to moisten the buccal mucosa in patients with a dry mouth.
- *Effentora*® buccal tablets can be placed sublingually if necessary.
- Fentanyl exposure from *Instanyl*® is unaffected by the common cold (providing nasal vasoconstrictors are not co-administered).
- Before using *Instanyl*® for the first time, the nasal spray must be primed until a fine mist appears; 3–4 actuations of the nasal spray are usually required. If the product has not been used during a period of >7 days, the nasal spray must be actuated once before the next dose is taken.
- Prior to using *PecFent*®, the bottle must be primed until a green bar appears in the counting window (should occur after four sprays). For the 8-spray bottle, if the product has not been used for >5 days, it should be reprimed by spraying once. The bottle should be discarded 60 days after first use.
- Patients should not blow their nose immediately after *PecFent*® administration.
- Patients must be advised that they may not feel the spray being administered, and that they should rely on the audible click and the

number on the counter advancing to confirm that a spray has been delivered (*PecFent®*).

- Concurrent use of nasally administered products (including OTC products) on the effectiveness of *Instanyl®* or *PecFent®* has not been studied.

Pharmacology

Refer to *Fentanyl (transdermal/parenteral*, p. 270*)*.

Reference

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.

Finasteride

Proscar® (POM)

Tablet: 5mg (28).

Generic (POM)

Tablet: 5mg (28).

Indications

- Benign prostatic hyperplasia (BPH).

Contraindications and cautions

- Finasteride has been linked to depression. Patients should be advised to stop finasteride immediately and inform a healthcare professional.
- Breast cancer has been reported in men receiving finasteride. Patients should be instructed to inform a healthcare professional about any changes in their breast tissue such as lumps, pain, gynaecomastia, or nipple discharge.
- Patients with large residual urine volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy.
- Finasteride causes a decrease in serum prostate-specific antigen concentrations by approximately 50% in patients with BPH, even in the presence of prostate cancer. Reference values may need adjustment.
- Women who are pregnant or may become pregnant should not handle crushed or broken finasteride tablets because of the potential risk to a male fetus.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: decreased libido; decreased volume of ejaculate; impotence.
- *Uncommon*: breast enlargement; breast tenderness; ejaculation disorder; rash.
- *Unknown*: depression; erectile dysfunction (may continue after discontinuation); hypersensitivity reactions; increased liver enzymes; palpitation; testicular pain.

Drug interactions

- Finasteride is metabolized by CYP3A4, but no clinically important drug interactions have been identified. Nonetheless, co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Dose

- 5mg PO OD.

Dose adjustments

Elderly

- No dosage adjustments necessary.

Hepatic/renal impairment

- There are no specific dose recommendations for use in liver impairment; the manufacturer states there are no data available in patients with hepatic insufficiency.
- Dosage adjustments are unnecessary in patients with renal impairment.

Additional information

- Although tablets may be crushed and dispersed in water prior to administration, it is not recommended to be performed due to the risk of exposure.

Pharmacology

Finasteride is a competitive and specific inhibitor of 5α-reductase, an intracellular enzyme that converts testosterone into the more potent dihydrotestosterone (DHT). Inhibition results in significant decreases in serum and tissue DHT concentrations.

Fluconazole ♥

Diflucan® (POM)

Capsule: 50mg (7); 150mg (1); 200mg (7).
Suspension: 50mg/5mL (35mL); 200mg/5mL (35mL).
Infusion solution: 200mg/100mL (1).

Generic (POM)

Capsule: 50mg (7); 150mg (1); 200mg (7).
Suspension: 50mg/5mL (35mL).
Infusion bags: 200mg/100mL (5); 400mg/200mL (5).
Infusion solution: 50mg/25mL (1); 200mg/100mL (1; 5).
NB—capsules may be sold in pharmacies for genital candidosis in those aged 16–60 years at a maximum dose of 150mg.

Indications

- Mucosal candidosis (including oropharyngeal and oesophageal).
- Genital candidosis.
- For other fungal infections, seek local microbiological advice.

Contraindications and precautions

- Post-marketing surveillance has identified very rare cases of QT prolongation and TdP. Many cases involved seriously ill patients with multiple risk factors. Nonetheless, there is a *known* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 292)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - use with caution in patients with significant bradycardia and in those with recent acute myocardial infarction or uncompensated heart failure.
- Patients may develop abnormal LFTs during fluconazole therapy. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Fluconazole can rarely cause exfoliative skin reactions. If a rash develops in a patient with:
  - a superficial fungal infection, treatment should be discontinued
  - invasive/systemic fungal infections, treatment should be closely monitored and discontinued if bullous lesions or erythema multiforme develop; discuss with the local microbiology team.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; diarrhoea; headache; raised liver enzymes; nausea; rash; vomiting.

- *Uncommon*: anaemia; reduced appetite; asthenia; cholestasis; constipation; dizziness; drowsiness; dry mouth; dysgeusia; dyspepsia; fatigue; flatulence; insomnia; jaundice; malaise; myalgia; paraesthesia; pruritus; seizures; sweating; urticaria; vertigo.
- *Rare*: alopecia; anaphylaxis; angioedema; blood dyscrasias (e.g. leucopenia, thrombocytopenia); hepatitis; hypercholesterolaemia; hypertriglyceridaemia; hypokalaemia; QT prolongation; skin reactions (Stevens–Johnson syndrome; toxic epidermal necrolysis); TdP; tremor.
- *Not known*: DRESS.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Fluconazole is a potent inhibitor of CYP2C19 and a moderate inhibitor of CYP2C9; at higher doses (>200mg/day), it inhibits CYP3A4. Interactions are less likely to be clinically relevant with a single-dose course of treatment (e.g. 150mg for genital candidosis). Co-administration with drugs that are metabolized by these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Enzyme inhibition is likely to persist for up to 4–5 days after discontinuation due to the long half-life.*
- *Alfentanil*—metabolism may be inhibited (although more likely to occur when fluconazole doses are >200mg daily).
- *Amitriptyline*—increased risk of adverse effects due to inhibition of metabolism; other factors may be necessary before this interaction becomes significant (e.g. co-administration of other interacting drugs).
- *Calcium channel blockers*—increased risk of adverse effects due to inhibition of CYP3A4 (fluconazole doses >200mg daily); dose adjustments may be necessary.
- *Carbamazepine*—increase in adverse effects possible due to inhibition of CYP3A4.
- *Celecoxib*—increased plasma levels due to inhibition of CYP2C9; halve the celecoxib dose if combination necessary.
- *Ciclosporin*—increased concentration of ciclosporin (refer to the SmPC).
- *Citalopram*—serotonin syndrome has been reported with this combination (CYP2C19 inhibition).
- *Cyclophosphamide*—possible reduced effect due to a decrease in the formation of active metabolite via CYP2C9.
- *Fentanyl*—metabolism may be inhibited (although more likely to occur when fluconazole doses are >200mg daily).
- *β-hydroxy β-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors*—increased risk of myopathy and rhabdomyolysis.
- *Losartan*—fluconazole inhibits formation of active metabolite.
- *Methadone*—fluconazole may enhance serum concentration of methadone.

- *Midazolam*—increased sedative effects due to CYP3A4 inhibition (although more likely to occur when fluconazole doses are >200mg daily).
- *Naloxegol*—risk of increased exposure to naloxegol; use lower dose of naloxegol; avoid combination at higher doses of fluconazole (i.e. >200mg/day).
- *NSAIDs*—fluconazole can increase serum concentration of several NSAIDs metabolized by CYP2C9 (e.g. diclofenac, naproxen).
- *Phenobarbital*—risk of increased exposure to phenobarbital.
- *Phenytoin*—risk of increased exposure to phenytoin; consider alternative treatment or closely monitor phenytoin plasma concentration.
- *Rifampicin*—reduces the plasma concentration of fluconazole.
- *Sertraline*—risk of increased exposure to sertraline.
- *Warfarin*—anticoagulant effect potentiated in dose-related manner; patient should be closely monitored and the warfarin dose adjusted accordingly.

Pharmacodynamic

- Fluconazole has been associated with prolongation of the QT interval. Concurrent use of fluconazole with erythromycin and quinidine is specifically contraindicated by the manufacturer. There is a potential risk that co-administration with other drugs (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *haloperidol*, *methadone*, *quinine*) that also prolong the QT interval may result in ventricular arrhythmias.

Dose

Mucosal candidosis

- 50mg PO OD for 7–14 days.
- Dose may be increased as appropriate to 100mg PO OD in difficult cases.
- In oesophagitis, duration of treatment may need to be up to 30 days.
- [+]150mg PO as a single dose has been reported in one study[(1)] to be an effective treatment of mucosal candidosis for patients with advanced cancer.

Genital candidosis

- 150mg PO as a single dose.

Dose adjustments

Elderly

- No dose adjustments necessary.

Hepatic/renal impairment

- Adjustments to single-dose therapy are not necessary.
- There are limited data pertaining to use in hepatic impairment and the manufacturer advises caution. While fluconazole is excreted predominantly in the urine as unchanged drug, due consideration should be given to the inhibitory effects on CYP2C9 and CYP2C19 (and CYP3A4 at higher doses) with concurrent drugs.

- In patients with impaired renal function, the normal dose should be used on day 1; subsequent doses are based on the degree of renal impairment, as shown in Table 3.11.

Table 3.11 Dose adjustments of fluconazole according to renal impairment

Creatinine clearance (mL/min)	Percentage of recommended dose
>50	100%
≤50 (no haemodialysis)	50%
Regular haemodialysis	100% after each dialysis (on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance)

Additional information

- In general, the treatment of choice for mild oral candidosis is *nystatin*.
- The oral suspension may be a preferable formulation for the treatment of oral candidosis.
- Resistance to fluconazole is a problem and should be borne in mind in apparent cases of treatment failure.
- Be aware of the potential for drug interactions with fluconazole.

Pharmacology

The mechanism of action of fluconazole is believed to be through an increase in permeability of the cell membrane. The resulting damage leads to leakage of cellular contents and prevention of uptake of essential molecules. Fluconazole is not greatly affected by enzyme induction/inhibition since the majority of a dose is excreted unchanged in the urine.

Reference

1. Lagman R, Davis M, LeGrand S, *et al*. Single-dose fluconazole therapy for oral thrush in hospice and palliative medicine patients. *Am J Hosp Palliat Care*. 2017;**34**(7):645–9.

Flumazenil

Generic (POM)
Injection: 500 micrograms/5mL (5).

Indications

- Reversal of sedative effects of benzodiazepines.

Contraindications and cautions

- Flumazenil is contraindicated in patients receiving a benzodiazepine for control of a potentially life-threatening condition (e.g. control of intracranial pressure or status epilepticus).
- Use with caution in epileptic patients receiving benzodiazepines as abrupt cessation of effect may precipitate a seizure.
- Use with caution in patients with hepatic impairment (see *Dose adjustments*, p. 296).
- In cases of mixed intoxications (e.g. with TCAs), excessive benzodiazepine doses may have a protective effect. Flumazenil should not be used to reverse the effects of benzodiazepines if there is associated autonomic (anticholinergic), neurological (motor abnormalities), or CV symptoms as a result of TCA toxicity.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: nausea; vomiting.
- *Uncommon*: anxiety and/or fear; palpitations (all usually following rapid injection).
- *Not known*: flushing; panic attacks (in patients with a history of panic reactions); seizures (particularly in patients known to suffer from epilepsy or severe hepatic impairment); withdrawal symptoms (e.g. agitation, anxiety, emotional lability, confusion, sensory distortions), following rapid injection of doses of 1mg or more in patients with high-dose and/or long-term exposure to benzodiazepines.

Drug interactions

Pharmacokinetic

- None known.

Pharmacodynamic

- *Benzodiazepines*—reversal of effect.
- *Zolpidem/zopiclone*—reversal of effect.

Dose

- *Follow local guidelines or policies*.
- The licensed dose schedule is shown here:
  - 200 micrograms slow IV injection in 15 seconds
  - if desired level of consciousness is not obtained within 60 seconds, a further IV dose of 100 micrograms should be given and repeated at 60-second intervals to a maximum dose of 1mg IV (or 2mg IV if in intensive care)
  - usual dose needed is 300 micrograms to 600 micrograms.

Dose adjustments

Elderly

- No specific guidance available. Titrate dose to effect.

Hepatic/renal impairment

- No specific guidance is available for use in hepatic impairment. However, the manufacturer advises caution in hepatic impairment due to hepatic metabolism of flumazenil. In any event, the dose is titrated to effect.
- No dose adjustments are necessary in renal impairment.

Additional information

- If drowsiness recurs, an infusion of 100 to 400 micrograms/hr may be used. The rate of infusion is individually determined.

Pharmacology

Flumazenil antagonizes the actions of drugs that act via benzodiazepine receptors in the CNS.

Fluoxetine ♡

Prozac® (POM)

Capsule: 20mg (30).
Liquid: 20mg/5mL (70mL).

Generic (POM)

Tablet: 10mg (30).
Dispersible tablet: 20mg (28)—available as *Olena®*.
Capsule: 10mg (30); 20mg (30); 30mg (30); 40mg (30); 60mg (30).
Oral solution: 20mg/5mL (70mL) (*NB—some formulations are sugar-free; refer to individual SmPCs*).

Indications

- Depression.
- Obsessive–compulsive disorder (not discussed).

Contraindications and cautions

- Fluoxetine is contraindicated for use with an irreversible MAOI or within 14 days of stopping one. At least 5 weeks should elapse after discontinuing fluoxetine treatment before starting a MAOI.
- Although the combination of MAO-B selective inhibitors *rasagiline* and *selegiline* with SSRIs is well tolerated, there have been case reports of serotonin syndrome. If such a combination is necessary, the recommendation is to use *citalopram* or *sertraline* without exceeding recommended doses.[1] The SmPC states the dose of selegiline should not exceed 10mg PO OD.
- In the case of serious infection, *linezolid* (a reversible, non-selective MAOI) may be given with fluoxetine, but the patient must be closely monitored for symptoms of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29).
- The SmPC recommends alternate day dosing in patients receiving concomitant medication that may affect fluoxetine levels (i.e. strong CYP2D6 and CYP2C9 inhibitors).
- Serotonin toxicity has been reported in patients using SSRIs. Fluoxetine should be discontinued immediately if this is suspected and supportive symptomatic treatment should be initiated. Fluoxetine should not be used concomitantly with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 299).
- Fluoxetine inhibits the metabolism of *tamoxifen* via CYP2D6 (reducing the concentration of the active metabolite endoxifen). Wherever possible, avoid this combination.
- The SmPC states that combination with *metoprolol* (in cardiac failure) is contraindicated since the effect of metoprolol may be excessive due to CYP2D6 inhibition by fluoxetine.
- There is a *conditional* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 299)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome

  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - use with caution in patients with significant bradycardia and in those with recent acute myocardial infarction, uncompensated heart failure, or hepatic impairment (increased exposure to fluoxetine—see *Dose adjustments*, p. 301).
- Use with caution in epilepsy. SSRIs are, however, considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy. Fluoxetine is a CYP2C19 inhibitor and may affect phenytoin levels (see *Drug interactions*, p. 299).
- In addition, use with caution in
  - diabetes (SSRIs can alter glycaemic control and may cause impaired awareness of hypoglycaemia)
  - elderly (greater risk of hyponatraemia)
  - glaucoma (risk of mydriasis)
  - hepatic impairment (see *Dose adjustments*, p. 301).
- May precipitate psychomotor restlessness, which usually appears during early treatment.
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Fluoxetine may increase the risk of haemorrhage. Use with caution in patients with bleeding disorders or concurrent use with other drugs carrying a similar risk (see *Drug interactions*, p. 299).
- Some patients may experience increased anxiety symptoms at the beginning of treatment. This paradoxical reaction usually subsides within 2 weeks during continued treatment. A low starting dose is advised to reduce the likelihood of this effect.
- There is an increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs. The mechanism is unknown.
- Withdrawal symptoms can occur. Agitation, anxiety, asthenia (weakness), dizziness, headache, nausea/vomiting, sensory disturbances (e.g. paraesthesia), sleep disturbances (e.g. insomnia, intense dreams), and tremor are the most commonly reported reactions. They usually occur within the first few days of discontinuing treatment. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, although some may persist for up to 3 months or longer. While it is advised that fluoxetine is gradually tapered over 1–2 weeks, it has a longer plasma half-life than other SSRIs and seems to be associated with a lower incidence of withdrawal symptoms; discontinuation without tapering can be considered. See Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: diarrhoea; fatigue; headache; insomnia; nausea.
- *Common*: abnormal dreams; anxiety; decreased appetite; arthralgia; attention disorder; dizziness; drowsiness; dry mouth; dysgeusia; dyspepsia; flushing; gynaecological bleeding (e.g. menorrhagia, uterine bleeding); hyperhidrosis; lethargy; palpitations; pruritus; prolonged QT interval; rash; restlessness; sexual dysfunction (ejaculation disorder, erectile dysfunction, reduced libido); sleep disorder; tremor; urinary frequency; urticaria; visual disturbances (blurred vision); vomiting; decreased weight; yawning.
- *Uncommon*: abnormal thinking; alopecia; ataxia; balance disorder; bruxism; depersonalization; dyskinesia; dysphagia; dyspnoea; dysuria; elevated mood; euphoria; haemorrhage (e.g. epistaxis, GI); hypotension; increased liver enzymes; malaise; memory impairment; myoclonus; psychomotor restlessness; sexual dysfunction (e.g. abnormal orgasm, anorgasmia); suicidal behaviour; tinnitus; visual disturbances (mydriasis).
- *Rare*: aggression; agitation; akathisia; anaphylaxis; blood dyscrasias (e.g. leucopenia, neutropenia, thrombocytopenia); confusion; convulsion; dysphemia; hallucinations; hypomania; hyponatraemia/SIADH; mania; myalgia; panic attacks; pharyngitis; photosensitivity; sexual dysfunction (e.g. galactorrhoea, hyperprolactinaemia, priapism); serotonin syndrome; TdP; urinary retention; vasculitis.

Drug interactions

The long elimination half-lives (plasma concentrations detectable for up to 5–6 weeks after withdrawal) of both fluoxetine and its metabolite norfluoxetine should be borne in mind when considering pharmacokinetic and/or pharmacodynamic drug interactions.

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Fluoxetine is a strong inhibitor of CYP2D6 and *may* moderately inhibit CYP2C19. It is a substrate of CYP2C9 and CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➲ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Be mindful of CYP2D6 inhibition when switching antidepressants (see ➲ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74).
- *Carbamazepine*—potential risk of carbamazepine toxicity possibly due to CYP2C19 inhibition. Possible reduction in effect of fluoxetine due to CYP2C9 induction.
- *Codeine*—reduced analgesic benefit due to CYP2D6 inhibition.

- *Fluconazole*—risk of fluoxetine toxicity due to inhibition of CYP2C9.
- *Haloperidol*—increased risk of adverse effects from both drugs due to CYP2D6 inhibition.
- *Metoprolol*—risk of adverse effects due to CYP2D6 inhibition by fluoxetine (see ➔ *Contraindications and cautions*, p. 297).
- *Risperidone*—increased risk of adverse effects due to CYP2D6 inhibition by fluoxetine.
- *Phenytoin*—risk of phenytoin toxicity.
- *Tamoxifen*—possible reduced efficacy of tamoxifen; avoid combination.
- *Tramadol*—reduced analgesic benefit due to CYP2D6 inhibition.

Pharmacodynamic

- Risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 297)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *TCAs*, *tapentadol*, *tramadol*, *trazodone*.
- Fluoxetine is associated with a conditional risk of prolongation of the QT interval. There is a potential risk that co-administration with other drugs that prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 297).
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.
- *Antidiabetics*—increased risk of hypoglycaemia and impaired awareness of hypoglycaemia.
- *Antipsychotics*—increased risk of seizures.
- *Carbamazepine*—increased risk of hyponatraemia.
- *Cyproheptadine*—may reduce the antidepressant effects of fluoxetine.
- *Diuretics*—increased risk of hyponatraemia.
- *Lithium*—may enhance the effect of SSRIs.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).
- *NSAIDs*—increased risk of GI bleeding (potentially worse with aspirin and naproxen).
- *SNRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

- Initial dose 20mg PO OD, increased if necessary after 3–4 weeks of initiation of treatment and subsequently as judged clinically appropriate to a maximum of 60mg PO OD.

Dose adjustments

Elderly

- No specific dose reductions are necessary, but the elderly may tolerate lower doses better. Generally, 40mg PO OD should not be exceeded.

Hepatic/renal impairment

- In significant hepatic impairment, a lower dose or alternate day dosing is recommended (e.g. 20mg PO ALT DIE). SSRIs can increase the risk of GI bleeding from varices.
- A dose reduction is considered unnecessary in patients with impaired renal function. Nonetheless, fluoxetine may not be the most appropriate choice due to its extended half-life and interaction potential.

Additional information

- Fluoxetine and norfluoxetine have long half-lives that may minimize the risk of withdrawal symptoms after sudden cessation of treatment. Gradual reduction of the dose is generally unnecessary. If, however, withdrawal symptoms are apparent, resuming the previous dose and instigating a more gradual withdrawal is advised.
- Fluoxetine should be administered as a single dose during or between meals. If adverse effects are troublesome, the dose can be divided. If insomnia is a problem, give the dose in the morning.
- Some oral liquid formulations (including *Prozac*®) contain 3g sucrose/5mL.

Pharmacology

Fluoxetine is a selective inhibitor of serotonin reuptake and acts as an antagonist at the 5-HT_{2C} receptor. This latter effect may cause the alerting effect that patients report, even after the first dose. It has almost no affinity for adrenergic, dopaminergic, histaminergic, muscarinic, or other serotonergic receptors. Fluoxetine is well absorbed from the GI tract after oral administration. It is extensively metabolized by the polymorphic enzymes CYP2D6 and CYP2C9, with minor metabolic pathways involving CYP2C19 and CYP3A4/5. Fluoxetine also significantly inhibits CYP2D6, as well as moderately inhibiting CYP2C19. There is one active metabolite, norfluoxetine, which is also a CYP2D6 inhibitor and contributes to the overall pharmacodynamic profile of fluoxetine.

The elimination half-life of fluoxetine is 4–6 days, and norfluoxetine 4–16 days. These long half-lives are responsible for persistence of the drug for 5–6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney.

Reference

1. Aboukarr A, Giudice M. Interaction between monoamine oxidase B inhibitors and selective serotonin reuptake inhibitors. *Can J Hosp Pharm.* 2018;**71**(3):196–207.

Flutamide ♡

Generic (POM)
Tablet: 250mg (84).

Indications

- Advanced prostate cancer.

Contraindications and cautions

- Use with caution in hepatic impairment—flutamide is associated with hepatic toxicity.
- Must not be used in patients with serum transaminase levels exceeding 2–3 times the upper limit of normal.
- LFTs should be checked monthly for first 4 months of treatment and periodically thereafter.
- Patients should be advised to seek medical attention at the first sign or symptom of liver impairment (e.g. pruritus, dark urine, jaundice).
- Avoid excessive alcohol consumption.
- Avoid combination with CYP1A2 inhibitors (see ➔ *Drug interactions*, p. 303).
- Although not mentioned by *CredibleMeds®*, the SmPC states androgen deprivation therapy may prolong the QT interval (post-marketing experience). There is a possible risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 303)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- Use with caution in patients with a history of CV disease:
  - flutamide may exacerbate oedema or ankle swelling in patients prone to these conditions
  - there is a risk of thromboembolism as flutamide causes an increase in oestradiol levels.
- Use with caution in renal impairment (see ➔ *Dose adjustments*, p. 303).
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: breast tenderness; galactorrhoea; gynaecomastia.
- *Common*: increased appetite; diarrhoea; drowsiness; hepatitis; insomnia; nausea; vomiting.
- *Rare*: anorexia; anxiety; asthenia; constipation; depression; dizziness; dyspepsia; headache; hot flushes; hypertension; interstitial pneumonitis; liver enzyme changes; lymphoedema; malaise; oedema; pruritus; thirst; urticaria; visual disturbance (blurred vision).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized by CYP1A2 to an active metabolite. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Theophylline*—cases of theophylline toxicity reported.

Pharmacodynamic

- Androgen deprivation therapy may prolong the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.

Dose

- 250mg PO TDS.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- No specific guidance is available for use in hepatic impairment. The manufacturer advises flutamide should only be administered after careful assessment of the individual benefits and risks.
- No specific guidance is available for use in renal impairment. The manufacturer advises caution in renal impairment but does not make a recommendation for dose adjustments. It is highly protein-bound and unlikely to be removed by dialysis. Approximately 45% of the administered dose is excreted in the urine.

Additional information

- Although tablets may be crushed and dispersed in water prior to administration, it is not recommended to be performed due to the risk of exposure.

Pharmacology

Flutamide is a non-steroidal anti-androgen that blocks the action of androgens of adrenal and testicular origin which stimulate the growth of normal and malignant prostatic tissue. It is completely absorbed following oral administration and is highly protein-bound. Flutamide is extensively metabolized by CYP1A2 to an active metabolite. The metabolites are eliminated via the kidneys and bile.

Furosemide ♡

Generic (POM)
Tablet: 20mg (28); 40mg (28; 1000); 500mg (28).
Oral solution: 20mg/5mL (150mL); 40mg/5mL (150mL); 50mg/5mL (150mL).
Injection: 20mg/2mL (10); 50mg/5mL (10); 250mg/25mL (10).

Indications

- Management of oedema associated with congestive heart failure, cirrhosis of the liver, or renal disease.
- Resistant hypertension.
- †Malignant ascites (associated with portal hypertension and a low albumin serum level).[1–3]

Contraindications and cautions

- Furosemide is contraindicated for use in the following conditions:
  - Addison's disease (hyponatraemia risk)
  - anuria or renal failure with anuria not responding to furosemide
  - dehydration
  - digoxin toxicity (see ➔ *Drug interactions*, p. 305)
  - hypersensitivity to sulfonamides
  - hypovolaemia
  - renal failure associated with hepatic coma
  - severe hypokalaemia or hyponatraemia
  - severe renal impairment (CrCl <30mL/min).
- The manufacturers of risperidone advise against concurrent use with furosemide due to increased risk of mortality.
- There is a *conditional* risk of QT prolongation/TdP (likely due to induced electrolyte disturbances):
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 305)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct significant electrolyte disturbances (e.g. hypokalaemia or hypomagnesaemia) before commencing treatment.
- Use with caution in the following:
  - bladder outflow obstruction (risk of urinary retention)
  - diabetes (may cause hyperglycaemia)
  - elderly (see ➔ *Dose adjustments*, p. 307)
  - gout (increased risk of hyperuricaemia)
  - hepatorenal syndrome
  - hypotension
  - hypovolaemia
  - nephrotic syndrome (the effect of furosemide may be reduced and its ototoxicity potentiated)
  - patients at risk of electrolyte imbalance
  - prostatic hypertrophy (risk of urinary retention).
- Oral solutions may contain up to 10% v/v of alcohol (refer to individual SmPCs).

- Furosemide should be discontinued prior to a glucose tolerance test.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: dehydration; hypocalcaemia; hypochloraemic metabolic alkalosis; hypomagnesaemia; hyponatraemia; hypotension (if severe, may cause signs and symptoms such as drowsiness, dry mouth, headache, impairment of concentration and reactions, light-headedness, visual disturbances, and weakness).
- *Common*: increased creatinine; hypochloraemia; hypovolaemia; increased serum urea.
- *Uncommon*: aplastic anaemia; cardiac arrhythmias; changes to serum cholesterol (reduction of serum high-density lipoprotein cholesterol, elevation of serum LDL cholesterol, elevation of serum triglycerides); constipation; deafness (often irreversible and associated with high-dose or rapid IV administration); diarrhoea; dry mouth; fatigue; gout; hyperglycaemia; hyperuricaemia; impaired glucose tolerance; muscle cramps; muscle weakness; nausea; thirst; urinary incontinence; vomiting.
- *Rare*: acute pancreatitis; acute renal failure; bone marrow depression (withdraw treatment); confusion; eosinophilia; headache; jaundice; leucopenia; paraesthesia; photosensitivity; pruritus; rash; tinnitus (associated with high-dose or rapid IV administration); toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- *Colestyramine*—reduced absorption of furosemide.
- *Lithium*—increased risk of lithium toxicity.
- *Phenytoin*—effect of furosemide reduced, possibly through an unknown effect on absorption.
- *Sucralfate*—reduced absorption of furosemide; not to be taken within 2 hours of each other.

Pharmacodynamic

- Cardiac toxicity may be increased by furosemide-induced hypokalaemia and/or hypomagnesaemia when co-administered with drugs associated with QT prolongation.
- *ACE-Is*—increased risk of hypotension.
- *Aminoglycosides*—furosemide may increase nephrotoxicity.
- *Antiarrhythmics*—risk of cardiac toxicity (hypokalaemia).
- *Antidiabetics*—hypoglycaemic effects antagonized by furosemide.
- *Antihypertensives*—increased risk of hypotension.

- *Antipsychotics*—increased risk of hypotension and cardiac toxicity with certain antipsychotics.
- *β_2-agonists*—increased risk of hypokalaemia.
- *Baclofen*—increased risk of hypotension.
- *Bisphosphonates*—risk of hypocalcaemia and dehydration.
- *Carbamazepine*—increased risk of hyponatraemia.
- *Corticosteroids*—increased risk of hypokalaemia; reduced diuretic effect.
- *Digoxin*—electrolyte disturbances (hypocalcaemia, hypokalaemia, hypomagnesaemia) increase toxicity.
- *Liquorice*—increased risk of hypokalaemia.
- *NSAIDs*—reduced diuretic effect; increased risk of renal impairment.
- *Reboxetine*—increased risk of hypokalaemia.
- *Theophylline*—increased risk of hypokalaemia.

Unknown

- *Risperidone*—increased risk of death in elderly patients with dementia.

Dose

Oral

Oral doses should be administered in the morning to avoid nocturnal diuresis.

Oedema

- Initial dose 40mg PO OM. Typical maintenance doses range from 20mg to 40mg PO OD. In resistant cases, this may be increased progressively to 80mg to 120mg PO OM (or split into morning and noon doses). Higher doses may be required.
- †Alternatively, 20mg to 40mg SUBLING OM (using tablet formulation) may be used.

Resistant hypertension

- 40mg to 80mg PO OM. Higher doses may be required.

†*Ascites*

- Use only in combination with spironolactone (see Chapter 3, *Spironolactone*, p. 633).
- Initial dose 40mg PO OM. Typical maintenance dose 20mg to 40mg PO OM. In resistant cases, this may be increased to 160mg PO OM, or higher in refractory cases.

Parenteral

IV furosemide must be injected or infused slowly; a rate of 4mg/min must not be exceeded.

Oedema

- By IM or slow IV injection of 20mg to 50mg, increased if necessary in steps of 20mg, not more frequently than every 2 hours. Doses above 50mg should be administered via slow IVI. Maximum 1.5 g daily.
- †Alternatively, 20mg to 140mg via CSCI over 24 hours can be used for management of end-stage congestive heart failure.

- [+]For patients already taking PO furosemide, the dose can be converted to CSCI, based on an oral bioavailability of 60–70%, although some use a 1:1 conversion.
- For practical reasons, the maximum dose that can be delivered per CSCI is 230mg (based on a maximum volume of 23mL in a 30mL syringe using the BD Bodyguard T (formerly CME T34) syringe pump). For higher doses, in order to avoid the need for two syringe pumps, it is possible to use a 50mL syringe on the BD BodyGuard T syringe pump, permitting up to 370mg (37mL) to be infused over 24 hours. [+]A lock box manufactured for the CME T60 will fit around the BodyGuard T syringe pump, with a 50mL syringe attached.

Dose adjustments

Elderly

- No specific guidance is available, but the dose should be titrated until the required response is achieved.

Hepatic/renal impairment

- Patients with hepatic impairment are more at risk of encephalopathy due to hypokalaemia, so other diuretics may be more appropriate. In alcoholic cirrhosis, the risk of hypomagnesaemia is increased, potentially leading to the development of arrhythmias.
- Patients with renal impairment may require higher doses (furosemide must be excreted in order to exert its effect).

Additional information

- Diuresis normally starts within 1 hour of oral administration and is regarded as complete after 6 hours.
- The kidney appears to develop tolerance to furosemide for 6 hours post-diuresis. It should therefore be given as a single daily dose in the morning *unless* the patient has an indwelling urinary catheter when it can be given BD (12 hours apart).
- Oral bioavailability of furosemide falls between 60% and 70%. Consider this when converting to IV or SUBCUT.
- Furosemide injection has an alkaline pH, so is unlikely to be compatible with many drugs. It is advisable to use a separate CSCI. However, furosemide is compatible with dexamethasone via CSCI.[4]

Pharmacology

Furosemide is a loop diuretic, which acts by inhibiting reabsorption of Na^+ and chloride in the ascending limb of the loop of Henle, leading to increased excretion of water and Na^+. Its mechanism of action involves inhibition of a Na^+/K^+/chloride co-transport system. K^+ secretion from the distal convoluted tubule is also increased due to exchange of K^+ for Na^+. Furosemide also increases excretion of bicarbonate, Ca^{2+}, hydrogen, Mg^{2+}, and phosphate.

References

1. Smith EM, Jayson GC. The current and future management of malignant ascites. *Clin Oncol*. 2003;**15**(2):59–72.

2. Husbands EL. Targeting diuretic use for malignant ascites—two case reports highlighting the value of the serum-ascites albumin gradient in a palliative setting. *J Pain Symptom Manage*. 2010;**39**(2):e7–9.
3. Singhal S, Baikati KK, Jabbour II, Anand S. Management of refractory ascites. *Am J Ther*. 2012;**19**(2):121–32.
4. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Gabapentin

Neurontin® (CD3 POM)
Capsule: 100mg (100); 300mg (100); 400mg (100).
Tablet (scored): 600mg (100); 800mg (100).

Generic (CD3 POM)
Capsule: 100mg (100); 300mg (100); 400mg (100).
Tablet: 600mg (100); 800mg (100).
Oral solution: 50mg/1mL (*sugar-free*; 150mL).

Indications

- Monotherapy and adjunctive treatment of partial seizures with or without secondary generalization.
- Peripheral neuropathic pain.
- †Hiccup.[1]
- †Insomnia.[2,3]
- †Pruritus.[4]
- †Restless legs syndrome.[5,6]
- †Sweats.[7,8]

Contraindications and cautions

- Gabapentin has been associated with a rare risk of respiratory depression. The following factors may increase the risk of this adverse effect:
  - compromised respiratory function
  - respiratory or neurological disease
  - renal impairment
  - use of concomitant CNS depressants (e.g. benzodiazepines; opioids—see ➔ *Drug interactions*, p. 310)
  - elderly.
- A population-based nested case-control study in patients receiving opioids reported an association between gabapentin dose (>900mg) and an increased risk of opioid-related mortality.[9] This may be explained by opioid-induced GI hypomotility and a possible increase in gabapentin absorption. Additionally, gabapentin may attenuate opioid tolerance, with consequential development of opioid adverse effects such as sedation and respiratory effects. Use of low initial doses and subsequent cautious titration are recommended. For this reason, a slower titration (than the licensed dose schedule) is recommended when gabapentin is added to a patient already receiving an opioid.
- Use with caution in patients with:
  - diabetes mellitus (may need to adjust hypoglycaemic treatment as weight gain occurs)
  - renal impairment (see ➔ *Dose adjustments*, p. 312).
- Avoid sudden withdrawal. Independent of indication, discontinue gradually over at least 1 week in order to avoid adverse effects such as nausea, vomiting, flu syndrome, anxiety, and insomnia. These withdrawal effects have been reported even after short-term use. In epileptic patients, abrupt withdrawal of anti-epileptics can precipitate status

epilepticus, although there is no evidence of rebound seizures with gabapentin.
- Patients should be monitored for signs of suicidal ideation since anti-epileptic drugs have been associated with this behaviour.
- Gabapentin can cause anaphylaxis, with symptoms such as difficulty breathing, swelling of the lips, throat, and tongue, and hypotension. The patient should be advised to stop taking gabapentin and seek immediate medical care.
- Severe, life-threatening systemic hypersensitivity reactions, such as DRESS, have been reported with gabapentin. The patient should be advised to report early manifestations of hypersensitivity, such as fever or lymphadenopathy, (with or without a rash) immediately.
- If affected by drowsiness and dizziness, patients should be warned about driving. Refer to Chapter 1, *Serotonin toxicity*, p. 29 for further details.

Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: ataxia; dizziness; drowsiness; fatigue; fever; viral infection.
- *Common*: acne; amnesia; anorexia; anxiety; arthralgia; asthenia; bronchitis; bruising; confusion; constipation; convulsions; cough; depression; diarrhoea; dry mouth; dyspepsia; dyspnoea; dysarthria; emotional lability; flatulence; flu syndrome; gingivitis; hostility; hypoesthesia; hyperkinesia; hypertension; increased appetite; leucopenia; malaise; myalgia; nausea; nervousness; nystagmus; oedema (facial, peripheral); otitis media; paraesthesia; pharyngitis; pneumonia; pruritus; rash; affected reflexes (absent, decreased, increased); respiratory infection; rhinitis; tremor; twitching; urinary tract infection; vasodilation; vertigo; visual disturbances (e.g. amblyopia, diplopia); vomiting; weight gain.
- *Uncommon*: agitation; allergic reactions (e.g. urticaria); elevated LFTs; hyperglycaemia (mainly in patients with diabetes); palpitations.
- *Rare*: hypoglycaemia (mainly in patients with diabetes); loss of consciousness; respiratory depression.
- *Unknown*: acute renal failure; alopecia; angio-oedema; breast hypertrophy; DRESS; dyskinesia; dystonia; erythema multiforme; gynaecomastia; hallucinations; hypersensitivity syndrome (including anaphylaxis); hyponatraemia; incontinence; myoclonus; pancreatitis (acute); rhabdomyolysis; sexual disorders (including changes in libido, ejaculation disorders, and anorgasmia); Stevens–Johnson syndrome; thrombocytopenia; tinnitus; withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- *Antacid* medication may reduce bioavailability by 20% or more. Gabapentin should be taken at least 2 hours following antacid administration.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *CNS depressants*—increased risk of CNS adverse effects.
- *Opioids*—possible opioid-sparing affect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.

Dose

Pain/epilepsy

- Table 3.12 shows both the licensed dose titration and a suggested dose titration. The licensed approach may be poorly tolerated by elderly patients or those receiving concurrent opioids, and for these patients, a more cautious titration is suggested. Whichever strategy is adopted, adverse effects are more common around the time of dose escalation but usually resolve in a few weeks. Slower titration may be preferred in the elderly or cancer population, although it may take longer to appreciate the therapeutic benefit.

Table 3.12 Licensed and suggested dose schedules for gabapentin

Licensed dose		Suggested dose	
Day 1	300mg PO ON	Day 1	100mg PO ON
Day 2	300mg PO BD	Day 2	100mg PO BD
Day 3	300mg PO TDS	Day 3	100mg PO TDS
Increase by 300mg PO OD, according to response, up to a maximum of 1200mg PO TDS.		Increase by 100mg PO TDS every 2 days, as needed, to a maximum of 1200mg PO TDS.	

+Hiccups

- Initial dose 100mg PO TDS to QDS and increase as necessary up to 1200mg/day. Treatment should be reviewed once hiccups have resolved, and gradual withdrawal planned.

+Insomnia

- Initial dose 100mg PO ON. Increase as necessary, or as tolerated, up to a usual maximum dose of 1800mg PO ON.

+Pruritus

- Titrate as for pain/epilepsy (see Table 3.12) to a daily maximum dose of 1800mg.

+Restless legs syndrome

- Limited evidence from case reports or small studies suggests a dose of 600mg/day initially, increasing as necessary to a maximum of 2400mg/day. For palliative care patients, however, a more cautious titration as per pain is suggested.

+*Sweats*

- Titrate as for pain/epilepsy (see Table 3.12) to a maximum of 1800mg daily.

Dose adjustments

Elderly

- The elderly are more at risk of adverse effects with gabapentin, including respiratory depression. A more cautious titration (see ➔ *Dose*) may be necessary, or a dose reduction due to renal impairment (see below) may be considered.

Hepatic/renal impairment

- No dose adjustment is required for patients with hepatic impairment.
- Dose adjustments are necessary for patients with renal failure or undergoing haemodialysis, as shown in Table 3.13. Adjust the starting dose as necessary.
- For patients undergoing haemodialysis:
  - anuric patients:
    - initial loading dose of 300mg to 400mg, then 200mg to 300mg of gabapentin following each 4 hours of haemodialysis. On dialysis-free days, there should be no treatment with gabapentin
  - renally impaired patients:
    - dose as per Table 3.13, based on CrCl. An additional 200mg to 300mg dose following each 4-hour haemodialysis treatment is recommended.

Table 3.13 Dose adjustments of gabapentin according to renal impairment

Creatinine clearance (mL/min)	Maximum daily dose
≥80	1200mg PO TDS
50–79	600mg PO TDS
30–49	300mg PO TDS
15–29	300mg PO OD
<15*	300mg PO ALT DIE to OD

* For patients with CrCl <15mL/min, the daily dose should be reduced in proportion to the CrCl (e.g. for a CrCl of 7.5mL/min, the patient should receive 50% of the daily dose that patients with a CrCl of 15mL/min receive).

Additional information

- Gabapentin is exempt from the safe custody arrangements under the Misuse of Drugs (Safe Custody) Regulations 1973. Prescription requirements are, however, necessary.
- In the absence of the oral solution, gabapentin capsules can be opened and the contents dispersed in water or fruit juice immediately prior to use.
- Neuropathic pain should improve within 1 week.

- There may be a reduction in anxiety within a few weeks, although the effect is not as pronounced as with pregabalin.
- With high doses, increasing the dosing frequency can improve tolerance, and possibly effect, due to the saturable nature of absorption (see ➔ *Pharmacology*).
- The improvement in sleep may not be as pronounced as with pregabalin.
- Several studies reviewing conversion of gabapentin to pregabalin predict that a rough ratio for conversion is about 6:1 gabapentin to pregabalin.[10]

➔ Pharmacology

Gabapentin was originally developed as an agonist of the $GABA_A$ receptor, but it is devoid of GABA effects. The analgesic benefit of gabapentin is due to its affinity for the $\alpha_2\delta$ subunit of N and P/Q voltage-dependent Ca^{2+} channels. Gabapentin binds to the $\alpha_2\delta$ subunit, effectively closing the channel and preventing the release of neurotransmitters and modulators. The system-L transporter, L-type amino acid transporter-1 (LAT1), facilitates the absorption of gabapentin, although the mechanism of absorption is saturable within the normal dosing range. Therefore, increasing the dose does not proportionally increase the amount absorbed. Gabapentin is largely excreted unchanged in the urine, so dose adjustment is needed in renal impairment.

References

1. Thompson DF, Brooks KG. Gabapentin therapy of hiccups. *Ann Pharmacother*. 2013;**47**(6):897–903.
2. Rosenberg RP, Hull SG, Lankford DA, *et al*. A randomized, double-blind, single-dose, placebo-controlled, multicenter, polysomnographic study of gabapentin in transient insomnia induced by sleep phase advance. *J Clin Sleep Med*. 2014;**10**(10):1093–100.
3. Liu GJ, Karim MR, Xu LL, *et al*. Efficacy and tolerability of gabapentin in adults with sleep disturbance in medical illness: a systematic review and meta-analysis. *Front Neurol*. 2017;**8**:316.
4. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol*. 2016;**75**(3):619–25.e6.
5. Gonzalez-Latapi P, Malkani R. Update on restless legs syndrome: from mechanisms to treatment. *Curr Neurol Neurosci Rep*. 2019;**19**(8):54.
6. Albanese A. Gabapentin improved sensory and motor symptoms in the restless legs syndrome. *BMJ Evidence-Based Medicine*. 2003;**8**(4):117.
7. Drewe J, Bucher KA, Zahner C. A systematic review of non-hormonal treatments of vasomotor symptoms in climacteric and cancer patients. *Springerplus*. 2015;**4**:65.
8. Porzio G, Aielli F, Verna L, *et al*. Gabapentin in the treatment of severe sweating experienced by advanced cancer patients. *Support Care Cancer*. 2006;**14**(4):389–91.
9. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case-control study. *PLoS Med*. 2017;**14**(10):e1002396.
10. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010;**49**(10):661–9.

Gliclazide

Standard-release

Diamicron® (POM)
Tablet (scored): 80mg (60).

Generic (POM)
Tablet: 40mg (28); 80mg (28; 60).

Modified-release

Diamicron® MR (POM)
Tablet: 30mg (28; 56).

Generic (POM)
Tablet: 30mg (28; 56); 60mg (28; 56).

Indications

- Type 2 diabetes mellitus.

Contraindications and cautions

- Gliclazide is contraindicated for use in the following:
  - concurrent use of *miconazole* (see ➔ *Drug interactions*, p. 315)
  - diabetic ketoacidosis
  - diabetic pre-coma and coma
  - hypersensitivity to sulfonylurea or sulphonamides
  - severe hepatic impairment (see ➔ *Dose adjustments*, p. 316)
  - severe renal impairment (see ➔ *Dose adjustments*, p. 316)
  - Type 1 diabetes.
- Use with caution in patients with:
  - concomitant use of CYP2C9 inducers/inhibitors (see ➔ *Drug interactions*, p. 315)
  - G6PD deficiency
  - hepatic and/or renal impairment (see ➔ *Dose adjustments*, p. 316)
  - porphyria (acute porphyria has been described with some other sulfonylurea drugs in patients who have porphyria).
- Avoid alcohol as this can enhance the hypoglycaemic response and lead to the onset of hypoglycaemic coma.
- The risk of hypoglycaemia increases with:
  - adrenal insufficiency
  - hepatic impairment
  - hypopituitarism
  - renal impairment.
- Patients must have a regular carbohydrate intake, avoid skipping meals, and ensure a balance between physical exercise and carbohydrate intake.
- Patients should be aware of the symptoms of hypoglycaemia and be careful about driving and use of machinery.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- hypoglycaemia (especially if meals skipped; dose-dependent), with associated symptoms such as aggression, agitation, confusion, headache, intense hunger, lassitude, poor concentration, reduced awareness, and slowed reactions.
- GI disturbances can also occur, including abdominal pain, constipation, diarrhoea, dyspepsia, and nausea and vomiting. Such symptoms can be avoided or minimized if gliclazide is taken with breakfast.
- More rarely reported adverse effects include:
  - anaemia; angio-oedema; erythema; hepatitis; hyponatraemia; jaundice; leucopenia; pruritus; rash; Stevens–Johnson syndrome; thrombocytopenia; toxic epidermal necrolysis; transient visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- The metabolism of gliclazide appears to be mediated mainly via CYP2C9. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Fluconazole*—can enhance hypoglycaemic effect (through CYP2C9 inhibition).
- *Miconazole*—contraindicated for use (enhanced hypoglycaemic effect, presumably CYP2C9 inhibition).
- *Warfarin*—increased risk of hypoglycaemia.

Pharmacodynamic

- *ACE-Is*—increased risk of hypoglycaemia.
- *Alcohol*—increases hypoglycaemic reaction, leading to onset of hypoglycaemic coma.
- *β_2-agonists*—hypoglycaemic effect may be antagonized.
- *Corticosteroids*—hypoglycaemic effect antagonized.
- *Diuretics*—hypoglycaemic effect may be antagonized.
- *SSRIs*—increased risk of hypoglycaemia.

Dose

Standard-release

- Initial dose 40mg to 80mg PO OD. Dose can be increased as necessary up to 160mg as a single daily dose, with breakfast. Higher doses must be administered in divided doses. Maximum dose 320mg daily.

Modified-release

- Initial dose 30mg PO OD with breakfast. Dose can be adjusted according to response every 4 weeks, or after 2 weeks if no decrease in blood glucose. Maximum dose 120mg daily.

NB—gliclazide modified-release 30mg may be considered to be approximately equivalent in therapeutic effect to standard-formulation gliclazide 80mg.

Dose adjustments

Elderly

- Usual adult doses can be used. Dose should be titrated to effect.

Hepatic/renal impairment

- Care should be exercised in patients with hepatic and/or renal impairment and a smaller initial dose should be used, with careful patient monitoring. Dose should be titrated to effect.
- Patients with mild to moderate renal impairment may use the usual dosing regimen, with careful patient monitoring.
- In severe hepatic and renal impairment, insulin therapy should be used.

Additional information

- Standard-release tablets can be crushed and dispersed in water immediately prior to use.

Pharmacology

Gliclazide is a sulfonylurea which stimulates β-cells of the islets of Langerhans in the pancreas to release insulin. It also enhances peripheral insulin sensitivity. It restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. The metabolism of many sulfonylureas is catalysed by CYP2C9. While this has not been categorically shown for gliclazide, drug interactions would suggest this is the case.

Glimepiride

Generic (POM)
Tablet: 1mg (30); 2mg (30); 3mg (30); 4mg (30).

Indications

- Type 2 diabetes mellitus.

Contraindications and cautions

- Glimepiride is contraindicated for use in the following:
  - diabetic ketoacidosis
  - diabetic coma
  - hypersensitivity to sulfonylurea or sulphonamides
  - severe hepatic impairment (see ➔ *Dose adjustments*, p. 318)
  - severe renal impairment (see ➔ *Dose adjustments*, p. 318)
  - Type 1 diabetes.
- Use with caution in patients with:
  - concomitant use of CYP2C9 inducers/inhibitors (see ➔ *Drug interactions*, p. 318)
  - G6PD deficiency
  - hepatic and/or renal impairment (see ➔ *Dose adjustments*, p. 318)
  - porphyria (acute porphyria has been described with some other sulfonylurea drugs in patients who have porphyria).
- Avoid alcohol as this can enhance the hypoglycaemic response and lead to the onset of hypoglycaemic coma.
- The risk of hypoglycaemia increases with:
  - adrenal insufficiency
  - hepatic impairment
  - hypopituitarism
  - renal impairment.
- Patients must have a regular carbohydrate intake, avoid skipping meals, and ensure a balance between physical exercise and carbohydrate intake.
- The manufacturer recommends regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) during treatment.
- Patients should be aware of the symptoms of hypoglycaemia and be careful about driving and use of machinery.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Rare*: blood dyscrasias (e.g. thrombocytopenia, agranulocytosis, haemolytic anaemia); hypoglycaemia (especially if meals skipped; dose-dependent).
- *Very rare*: abdominal discomfort/distension; cholestatic jaundice; diarrhoea; hepatitis; hypersensitivity reaction (with associated dyspnoea, hypotension); hyponatraemia; leukocytoclastic vasculitis; nausea; vomiting.
- *Not known*: cross-allergenicity with sulfonylureas and sulphonamides; pruritus; rash; thrombocytopenia (severe); transient visual disturbances (due to changes in blood glucose).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Glimepiride is a substrate of CYP2C9. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Fluconazole*—increases the plasma concentration of glimepiride.
- *Warfarin*—increased risk of hypoglycaemia.

Pharmacodynamic

- *ACE-Is*—increased risk of hypoglycaemia.
- *β_2-agonists*—hypoglycaemic effect may be antagonized.
- *Corticosteroids*—hypoglycaemic effect antagonized.
- *Diuretics*—hypoglycaemic effect may be antagonized.
- *SSRIs*—increased risk of hypoglycaemia.

Dose

- Initial dose 1mg PO OD taken shortly before or during the first main meal. The dose can be increased by 1mg daily every 1–2 weeks to a usual maximum dose of 4mg PO OD. A dose of 6mg PO OD can be used in exceptional cases.

Dose adjustments

Elderly

- Usual adult doses can be used, and the dose should be titrated to effect.

Hepatic/renal impairment

- Care should be exercised in patients with hepatic and/or renal impairment. Dose should be titrated to effect.
- Glimepiride should be avoided in patients with severe hepatic and/or renal impairment and insulin treatment should be initiated.

Additional information

- Tablets can be crushed and dispersed in water immediately prior to administration if necessary.

Pharmacology

Glimepiride is a sulfonylurea which stimulates β-cells of the islets of Langerhans in the pancreas to release insulin. It also enhances peripheral insulin sensitivity. It restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. The metabolism of glimepiride is catalysed by CYP2C9.

Glipizide

Minodiab® (POM)
Tablet: 5mg (28).

Generic (POM)
Tablet: 5mg (28; 56).

Indications

- Type 2 diabetes mellitus.

Contraindications and cautions

- Glipizide is contraindicated for use in the following:
  - concurrent use of *miconazole* (see ➔ *Drug interactions*)
  - diabetic ketoacidosis
  - diabetic coma
  - hypersensitivity to sulfonylurea or sulphonamides
  - severe hepatic impairment (see ➔ *Dose adjustments*, p. 320)
  - severe renal impairment (see ➔ *Dose adjustments*, p. 320)
  - Type 1 diabetes.
- Avoid alcohol as this can enhance the hypoglycaemic response and lead to the onset of hypoglycaemic coma.
- The risk of hypoglycaemia increases with:
  - adrenal insufficiency
  - hepatic impairment
  - hypopituitarism
  - renal impairment.
- Patients must have a regular carbohydrate intake, avoid skipping meals, and ensure a balance between physical exercise and carbohydrate intake.
- Patients should be aware of the symptoms of hypoglycaemia and be careful about driving and use of machinery.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal discomfort; diarrhoea; hypoglycaemia (especially if meals skipped; dose-dependent); nausea.
- *Uncommon*: cholestatic jaundice; dizziness; drowsiness; eczema; tremor; vomiting.
- *Not known*: blood dyscrasias (e.g. thrombocytopenia, agranulocytosis, haemolytic anaemia); confusional state; constipation; headache; hepatitis; hypersensitivity reaction; hyponatraemia; malaise; transient visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Glipizide is a substrate of CYP2C9. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see

Inducers and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

- *Fluconazole*—increases plasma concentration of glipizide.
- *Miconazole*—contraindicated for use (enhanced hypoglycaemic effect, presumably CYP2C9 inhibition).
- *Warfarin*—increased risk of hypoglycaemia.

Pharmacodynamic

- *ACE-Is*—increased risk of hypoglycaemia.
- *β_2-agonists*—hypoglycaemic effect may be antagonized.
- *Corticosteroids*—hypoglycaemic effect antagonized.
- *Diuretics*—hypoglycaemic effect may be antagonized.
- *SSRIs*—increased risk of hypoglycaemia.

Dose

- Initial dose 2.5mg to 5mg PO OD, taken before breakfast or lunch. The dose can be increased as necessary by 2.5mg to 5mg PO OD over several days. The maximum recommended single dose is 15mg PO daily; doses above 15mg should be divided. The maximum daily dose is 20mg.

Dose adjustments

Elderly

- Usual adult doses can be used, although the elderly are more susceptible to adverse effects. The initial dose should be 2.5mg PO OD and should be titrated to effect.

Hepatic/renal impairment

- Care should be exercised in patients with hepatic and/or renal impairment and a smaller initial dose should be used, with careful patient monitoring. Dose should be titrated to effect.
- Glipizide should be avoided in patients with severe hepatic and/or renal impairment and insulin treatment should be initiated.

Additional information

- Tablets can be crushed and dispersed in water immediately prior to administration if necessary.

Pharmacology

Glipizide is a sulfonylurea which stimulates β-cells of the islets of Langerhans in the pancreas to release insulin. It also enhances peripheral insulin sensitivity. It restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. The metabolism of many sulfonylureas is catalysed by CYP2C9.

Glyceryl trinitrate

Rectogesic® (POM)
Rectal ointment: GTN 0.4% (30 g).

Generic (P)
Sublingual tablet: 300 micrograms (100); 500 micrograms (100); 600 micrograms (100).
NB—tablets should be stored in the original container and discarded 8 weeks from opening.
Proprietary formulations are available (see current BNF).
Other formulations are available (e.g. parenteral, transdermal) but are not discussed (see current BNF).

Indications

- Anal fissure.
- †Smooth muscle spasm pain (e.g. anus, oesophagus, rectum).
- Angina (*not discussed*).

Contraindications and cautions

- Contraindicated for use in the following:
  - anaemia (severe)
  - aortic and/or mitral stenosis
  - closed-angle glaucoma
  - concomitant use with phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil)
  - constrictive pericarditis
  - hypertrophic obstructive cardiomyopathy
  - hypotension
  - hypovolaemia
  - migraine or recurrent headache
  - raised intracranial pressure.
- Use with caution in patients with:
  - hypothermia
  - hypothyroidism
  - malnutrition
  - recent history of myocardial infarction
  - severe hepatic impairment
  - severe renal impairment
  - susceptibility to angle-closure glaucoma.
- Note that transdermal patches that contain metal must be removed before MRI (to avoid burns).
- Tolerance can rapidly develop with long-acting or transdermal nitrates, with consequential loss of effect. This can be prevented by adopting a 'nitrate-free' period of 4–8 hours each day.
- Dry mouth may reduce the effectiveness of transmucosal GTN.
- Can exacerbate the hypotensive effects of other drugs (see ➔ *Drug interactions*, p. 322).

- GTN may cause dizziness, light-headedness, and blurred vision, especially on first use. Patients should be advised not to drive (or operate machinery) if affected.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: headache (throbbing).
- *Common*: hypotension (associated symptoms include dizziness, facial flushing, nausea, and weakness).
- *Uncommon*: anal discomfort (rectal formulation); diarrhoea (rectal formulation); oral discomfort, e.g. stinging, burning (oral formulations); rectal bleeding (rectal formulation); site reaction (transdermal formulations); vomiting.
- *Rare*: tachycardia.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None known.

Pharmacodynamic

- *Alcohol*—potentiates the hypotensive effect of GTN.
- *Heparin*—the anticoagulant effect may be reduced by GTN; dose adjustment may be necessary.
- The risk of hypotension is increased if GTN is taken concurrently with the following drugs:
  - β-blockers
  - calcium channel antagonists
  - diuretics
  - haloperidol
  - levomepromazine
  - opioids
  - phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil)
  - TCAs.

Dose

Anal fissure

- Cover the finger that will apply the ointment with cling film or a finger cot.
- Apply a small amount (approximately 2.5cm, equivalent to 1.5mg GTN) intra-anally BD until the pain improves or for a maximum of 8 weeks.

†Oesophageal spasm

- 400 micrograms to 500 micrograms SUBLING 5–15 minutes before food.
- The tablet can be removed once the pain has subsided or headache develops.

Dose adjustments

Elderly

- No dose adjustment necessary.

Hepatic/renal impairment

- No specific guidance available. Manufacturers advise caution in patients with severe hepatic and/or renal impairment.

Additional information

- Headache is a common adverse effect. It can be managed with paracetamol. If it persists, the dose of GTN should be reduced, or treatment withdrawn.
- The rectal ointment should be applied using a finger covering such as cling film.
- An unlicensed formulation of GTN rectal ointment 0.2% may be available as a special order. This strength may be helpful if 0.4% causes unacceptable adverse effects.

Pharmacology

GTN is converted to NO *in vivo*, which causes a cascade of intracellular events, resulting in subsequent release of Ca^{2+} and relaxation of smooth muscle cells.

Glycopyrronium bromide

Sialanar® (POM)
Oral solution: 400 micrograms/mL (as glycopyrronium base 320 micrograms/mL) (250mL).

Generic (POM)
Tablet (scored): 1mg; 2mg.
Oral solution: 1mg/5mL (150mL).
Injection: 200 micrograms/mL (10 × 1mL; 10 × 3mL).
Powder: 3g.

Unlicensed (POM)
Oral solution or suspension: various strengths (prepared from injection, powder, or tablets).
See *Additional information*, p. 326 for supply issues.

Indications

- +Hypersalivation.[1]
- +Nausea and vomiting (associated with inoperable bowel obstruction).[2]
- +Smooth muscle spasm (e.g. bowel colic).[2]
- +Terminal secretions.[3,4]

Contraindications and cautions

- No absolute contraindications. However, it has potent peripheral anticholinergic activity and can predispose to tachycardia.
- Use with caution in patients with:
  - bladder outflow obstruction
  - cardiac arrhythmias
  - congestive heart failure
  - coronary artery disease
  - hypertension
  - myasthenia gravis (particularly larger doses—see below)
  - narrow-angle glaucoma
  - paralytic ileus
  - pyrexia (reduces sweating)
  - renal impairment (see *Dose adjustments*, p. 326)
  - thyrotoxicosis.
- *There are case reports that suggest glycopyrronium can be used cautiously to treat symptoms of terminal secretions in patients with myasthenia gravis.*[5,6]
- Glycopyrronium may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.
- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients. The risk of such effects is low with glycopyrronium, as it does not readily cross the blood–brain barrier.

Adverse effects

Refer to the SmPC for a full list of adverse effects. Peripheral antimuscarinic effects are expected with glycopyrronium. The frequency is not defined, but reported adverse effects include:

- confusion; difficulty in micturition; dizziness; drowsiness; dry mouth; inhibition of sweating; palpitations; tachycardia (*less likely, compared to atropine or hyoscine butylbromide*); visual disturbances.

Drug interactions

Pharmacokinetic

- Undergoes minimal hepatic metabolism; mostly excreted unchanged by the kidneys.
- No recognized pharmacokinetic interactions.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- The anticholinergic effect of glycopyrronium can be additive with that of other drugs and *may* precipitate delirium or cognitive impairment in susceptible patients.
- *β_2-agonists*—increased risk of tachycardia.
- *Cyclizine*—increased risk of anticholinergic adverse effects.
- *Domperidone*—prokinetic effect may be reduced.
- *Metoclopramide*—prokinetic effect may be reduced.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

†Terminal secretions

- Initial dose 200 micrograms SUBCUT 4-hourly PRN, or 600 micrograms via CSCI over 24 hours.
- Dose can be increased to a usual maximum of 1200 micrograms via CSCI over 24 hours. Doses above 1200 micrograms will increase the risk of adverse effects and the benefits are unknown.

†Hypersalivation

- Initial dose 200 micrograms PO TDS and increased every 2–3 days as necessary up to 1000 micrograms PO TDS. Higher doses have been used (e.g. 2000 micrograms PO TDS).

†Nausea and vomiting (associated with inoperable bowel obstruction)/smooth muscle spasm

- Note that use has been extrapolated from experience with hyoscine butylbromide. There is only one case report that describes the use of glycopyrronium in the management of bowel obstruction.[2]
- Initial dose 200 micrograms SUBCUT 4-hourly PRN, or 600 micrograms via CSCI over 24 hours.
- Dose can be increased to a maximum of 1200 micrograms via CSCI over 24 hours.
- Doses above 1200 micrograms will increase the risk of adverse effects and the benefits are unknown.

Dose adjustments

Elderly

- No specific guidance available. Use the lowest effective dose as the elderly may be more susceptible to adverse effects.

Hepatic/renal impairment

- No specific guidance available for use in either hepatic or renal impairment.
- Glycopyrronium accumulates in renal impairment; dosage adjustments may be necessary. For patients with severe renal impairment (CrCl <30mL/min), suggested maximum 100 micrograms SUBCUT 4-hourly PRN or 600 micrograms via CSCI over 24 hours.

Additional information

- Oral solutions are available, licensed for pathological drooling in children and adolescents (aged 3 years and older) and as an add-on therapy for adults in the treatment of peptic ulcer. Although licensed formulations should be used wherever possible, an oral solution or suspension can be prepared in several ways. For immediate use, the contents of an ampoule can be administered orally or via a PEG (using a filter needle). The tablets can also be dispersed in water prior to administration. Alternatively, a 500 micrograms/mL oral suspension can be extemporaneously prepared (shown to be stable for at least 90 days when stored in amber plastic bottles at room temperature).[7]
- Glycopyrronium is stated to be *chemically and physically* compatible under stated conditions with hydromorphone, ondansetron, and oxycodone. Under stated conditions, glycopyrronium has been shown to be physically compatible with alfentanil, clonazepam, codeine, hydromorphone, hyoscine hydrobromide, lidocaine, morphine sulfate, ondansetron, promethazine, and ranitidine. The stability of glycopyrronium is affected above pH 6, as ester hydrolysis can occur. There are incompatibility issues with dexamethasone, dimenhydrinate, and phenobarbital. There may be concentration-dependent compatibility issues with cyclizine (but less so than with hyoscine butylbromide–cyclizine).[8]

Pharmacology

Glycopyrronium is a quaternary ammonium antimuscarinic that inhibits the peripheral actions of acetylcholine (e.g. smooth muscle, cardiac muscle, atrioventricular node, exocrine glands). At higher doses, it may also block nicotinic receptors. Due to the polarity of the quaternary compound, it does not readily cross the blood–brain barrier and is unlikely to produce symptoms such as sedation or paradoxical agitation (see Chapter 3, *Hyoscine hydrobromide*, p. 346). However, it does not have a direct antiemetic action like hyoscine hydrobromide. Glycopyrronium is mainly excreted unchanged by the kidneys and lower doses may be required in renal impairment.

References

1. Arbouw MEL, Movig KLL, Koopmann M, *et al*. Glycopyrrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. *Neurology*. 2010;**74**(15):1203–7.
2. Davis MP, Furste A. Glycopyrrolate: a useful drug in the palliation of mechanical bowel obstruction. *J Pain Symptom Manage*. 1999;**18**(3):153–4.
3. Hugel H, Ellershaw J, Gambles M. Respiratory tract secretions in the dying patient: a comparison between glycopyrronium and hyoscine hydrobromide. *J Palliat Med*. 2006;**9**(2):279–84.
4. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev*. 2008;**1**:CD005177.
5. Spiess JL, Scott SD. Anticholinergic agents for the treatment of 'death rattle' in patients with myasthenia gravis. *J Pain Symptom Manage*. 2003;**26**(1):684–6.
6. Hindmarsh J, Everett P, Hindmarsh S, Lee M, Pickard J. Glycopyrrolate and the management of 'death rattle' in patients with myasthenia gravis. *J Palliat Med*. 2020;**23**(10):1408–10.
7. Cober MP, Johnson CE, Sudekum D, Penprase K. Stability of extemporaneously prepared glycopyrrolate oral suspensions. *Am J Health Syst Pharm*. 2011;**68**(9):843–5.
8. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Granisetron ♀

Generic (POM)
Tablet: 1mg (10); 2mg (5).
Injection: 1mg/mL (5).
***Sancuso®* (POM)**
Transdermal patch: 3.1mg/24 hours.

Indications

- Nausea and vomiting (treatment and prevention of CINV*/RINV; PONV).
- +Intractable nausea and vomiting.[1]

Contraindications and cautions

- Since granisetron increases large bowel transit time, use with caution in patients with signs of subacute bowel obstruction.
- There is a *possible* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 329)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- There is a potential risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when granisetron is used concomitantly with certain serotonergic drugs. Treatment should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Granisetron should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 329).
- Patients using *Sancuso®* should be told that showering or washing normally can be continued while wearing the patch, but activities such as swimming, strenuous exercise, or using a sauna should be avoided. Patients should also be advised to avoid exposing the patch application site to direct heat sources, such as hot water bottles, electric blankets, heat lamps, saunas, or baths, because of the risk of increased granisetron absorption.
- Granisetron may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: constipation; headache.
- *Common*: diarrhoea; insomnia; LFT elevation.
- *Uncommon*: extrapyramidal reactions; hypersensitivity (anaphylaxis, urticaria); QT prolongation; rash; serotonin syndrome.

* Sancuso® is only licensed for the prevention of CINV.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized by CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Carbamazepine*, *phenobarbital*, and *phenytoin* can reduce granisetron serum concentrations and reduce the effect.
- The effect of grapefruit juice on the absorption of granisetron is unknown.

Pharmacodynamic

- Granisetron *may* cause prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 328).
- Risk of serotonin syndrome with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *SSRIs*, *tapentadol*, *tramadol*, *trazodone*, *TCAs*.
- Granisetron increases bowel transit time. This effect can be enhanced by drugs such as *opioids*, *TCAs*, and *anticholinergics*.
- *Domperidone/metoclopramide*—granisetron reduces the prokinetic effect.
- *Paracetamol*—possible reduced analgesic benefit.

Dose

CINV and RINV

- 1mg PO BD or 2mg PO OD for up to 7 days following treatment.
- Alternatively, 1mg to 3mg IV OD. Further doses may be given, at least 10 minutes apart.
- The maximum daily dose of granisetron should not exceed 9mg PO/IV.
- For *Sancuso*®, one patch 24–48 hours before chemotherapy.
- The patch can be worn for a maximum of 7 days; it should be removed 24 hours after completion of chemotherapy.

PONV

- 1mg IV OD. Further doses may be given, at least 10 minutes apart; maximum daily dose 3mg.

†Intractable nausea and vomiting

- †1mg to 3mg via CSCI over 24 hours, increased to a maximum dose of 9mg daily.

Dose adjustments

Elderly

- No dosage adjustments are necessary.

Hepatic/renal impairment

- No dosage adjustments are necessary in hepatic or renal impairment. Nonetheless, since hepatic metabolism is important for the elimination of granisetron, the lowest effective dose should be used in patients with hepatic impairment.

Additional information

- 5-HT_3 antagonists differ in chemical structure, pharmacokinetics, and pharmacodynamics. There may be individual variation in response, and it may be worth considering an alternative 5-HT_3 antagonist if response to granisetron is not as expected.
- Treatment with granisetron should be used regularly for 3 days, and then the response assessed. Avoid using on a PRN basis.
- Granisetron is *chemically and physically* compatible under stated conditions with dexamethasone. Under stated conditions, granisetron is *physically* compatible with diamorphine, hydromorphone, levomepromazine, metoclopramide, octreotide, and oxycodone.[(2)]

Pharmacology

Granisetron is a selective 5-HT_3 receptor antagonist, blocking serotonin peripherally on vagal nerve terminals and centrally in the CTZ. It is particularly useful in the treatment of nausea/vomiting associated with serotonin release (e.g. damage to enterochromaffin cells due to bowel injury, chemotherapy, or radiotherapy). It has little or no affinity for other serotonin receptors (including 5-HT_2), dopamine D_2 receptors, α_1-, α_2-, or β-adrenoreceptors, and histamine H_1 receptors.

References

1. Buchanan D, Muirhead K. Intractable nausea and vomiting successfully related with granisetron 5-hydroxytryptamine type 3 receptor antagonists in palliative medicine. *Palliat Med*. 2007;**21**(8):725–6.
2. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Haloperidol ♥

Haldol® (POM)
Oral liquid: 2mg/mL (100mL—*sugar-free*).

Generic (POM)
Tablet: 500 micrograms (28); 1.5mg (28); 5mg (28); 10mg (28).
Injection: 5mg/mL (1mL × 10).
Oral solution (sugar-free): 5mg/5mL (100mL); 10mg/5mL (100mL).

Indications

NB—there are differences in licensed indications between the formulations.

- Acute treatment of delirium when non-pharmacological treatments have failed.
- Intractable hiccup.
- Persistent aggression and psychotic symptoms in patients with moderate to severe Alzheimer's dementia and vascular dementia when non-pharmacological treatments have failed and when there is a risk of harm to self or others (*NB—only the oral solutions state this indication in the SmPC*; see ➔ *Contraindications and precautions*).
- Psychosis.
- Restlessness and agitation in the elderly.
- †Nausea and vomiting in palliative care.
- †Terminal agitation.

Contraindications and precautions

⚠ Warning

- Antipsychotic drugs have been associated with an elevated risk of VTE. Several potential mechanisms have been described, including drug-induced sedation, obesity, hyperprolactinaemia, increased platelet aggregation (by 5-HT_2 antagonism), and elevation of antiphospholipid antibody.
- An increased risk of mortality has been consistently observed in elderly patients with dementia treated with antipsychotics. The mechanism of mortality may be CV in nature (e.g. arrhythmia/TdP susceptibility from QT prolongation or increased risk of VTE). Conventional antipsychotics (e.g. haloperidol) may carry a greater risk of mortality than second-generation antipsychotics (e.g. quetiapine, risperidone).
- Although oral solutions are indicated for management of behavioural symptoms of dementia, other drugs such as quetiapine, risperidone, or citalopram may be preferable. Refer to local guidance.
- Avoid adrenaline with haloperidol, as severe hypotension and tachycardia may result (see ➔ *Drug interactions*, p. 333) .

- Contraindicated in the following circumstances:
  - lesions of the basal ganglia
  - Lewy body dementia
  - Parkinson's disease.

- There is a *known* risk of QT prolongation/TdP (doses <2mg/day PO carry a reduced risk).[1] The SmPC contraindicates the use of haloperidol in the following situations:
  - arrhythmias treated with class IA and III antiarrhythmic medicinal products
  - clinically significant bradycardia
  - concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 333)
  - electrolyte disturbances (correct hypokalaemia or hypomagnesaemia before commencing treatment)
  - known QT interval prolongation or congenital long QT syndrome
  - recent acute myocardial infarction
  - second- or third-degree heart block
  - uncompensated heart failure.
- Haloperidol should be used with caution in the following circumstances:
  - atrial fibrillation (increased risk of CVA)
  - cardiac disease
  - co-administration of CYP2D6 and/or CYP3A4 inhibitors (see ➔ *Drug interactions*, p. 333)
  - diabetes (increased risk of CVA; may impair glycaemic control)
  - elderly (see ➔ *Dose adjustments*, p. 335)
  - epilepsy (lowered seizure threshold)
  - family history of QT prolongation
  - hepatic/renal impairment (see ➔ *Dose adjustments*, p. 335)
  - hypercholesterolaemia (increased risk of CVA)
  - hyperthyroidism (increased risk of haloperidol toxicity)
  - poor metabolizers of CYP2D6 (if aware)
  - uncontrolled hypertension (increased risk of CVA).
- Sudden cessation of smoking may lead to the development of adverse effects associated with excess dose (loss of CYP1A2 induction).
- Rapid discontinuation may lead to rebound worsening of symptoms (such as nausea, vomiting, and insomnia). Withdraw gradually whenever possible.
- Haloperidol has been associated with the development of akathisia, which is most likely to occur within the first few weeks of treatment. Review continued treatment as increasing the dose may be detrimental.
- If a patient develops signs and symptoms indicative of neuroleptic malignant syndrome (NMS), such as altered mental status, autonomic instability (e.g. cardiac dysrhythmia, diaphoresis), hyperpyrexia, and muscle rigidity, or presents with unexplained high fever without additional clinical manifestations of NMS, haloperidol must be discontinued.
- Haloperidol may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: agitation; extrapyramidal disorder; headache; hyperkinesia; insomnia.

- *Common*: akathisia; bradykinesia; constipation; depression; dizziness; drowsiness; dry mouth; dyskinesia; dystonia (including swallowing difficulties, tightness of the throat, and tongue protrusion); hypertonia; hypotension; abnormal LFTs; nausea/vomiting; oculogyric crisis; postural hypotension; rash; salivary hypersecretion; sexual dysfunction (*erectile dysfunction*); tardive dyskinesia; tremor; urinary retention; visual disturbance; weight changes (*decrease and increase*).
- *Uncommon*: amenorrhoea; breast discomfort; confusion; convulsion; dysmenorrhoea; dyspnoea; galactorrhoea; hepatitis; hyperhidrosis; hypersensitivity; hyperthermia; jaundice; leucopenia; muscle rigidity; muscle spasms; oedema; Parkinsonism; photosensitivity; pruritus; restlessness; sexual dysfunction (*loss of libido*); tachycardia; torticollis; urticaria.
- *Rare*: bronchospasm; hyperprolactinaemia; menorrhagia; muscle twitching; NMS; nystagmus; prolonged QT interval.
- *Not known*: akinesia; anaphylaxis; angioedema; blood dyscrasia (*agranulocytosis*, *neutropenia*, *pancytopenia*, *thrombocytopenia*); cogwheel rigidity; gynaecomastia; hepatic failure; hypoglycaemia; hypothermia; laryngeal oedema; sexual dysfunction (*priapism*); rhabdomyolysis; SIADH; TdP; ventricular tachycardia.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Haloperidol is metabolized by UGT2B7 (major), CYP2D6, and CYP3A4/5, with minor pathways involving UGT1A4, UGT1A9, and CYP1A2. It is an inhibitor of CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Carbamazepine*—increases the metabolism of haloperidol through UGT2B7 and CYP3A4/5 induction. Other CYP3A4/5 inducers may have the same effect. The haloperidol dose may therefore need to be increased, according to the patient's response.
- *Celecoxib*—increased risk of haloperidol adverse effects through inhibition of CYP2D6.
- *Ciprofloxacin*—increased risk of haloperidol adverse effects through inhibition of CYP3A4 (more likely in CYP2D6 poor metabolizers).
- *Fluoxetine*—increased risk of adverse effects from both drugs due to CYP2D6 inhibition.
- *Paroxetine*—increased risk of adverse effects from both drugs due to inhibition of CYP2D6.
- *Sertraline*—increased risk of haloperidol adverse effects through inhibition of CYP2D6.

- *Venlafaxine*—increased risk of adverse effects from both drugs due to CYP2D6 inhibition (may be of more significance for venlafaxine in CYP2D6 poor metabolizers).
- Avoid grapefruit juice, as it may increase the bioavailability of haloperidol through inhibition of intestinal CYP3A4/5.
- Smoking may lead to faster metabolism of haloperidol. Dose adjustments may be necessary upon smoking cessation (see Box 1.11).

Pharmacodynamic

- Haloperidol can cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *methadone*, *quinine*) may result in ventricular arrhythmias (see *Contraindications and precautions*, p. 331).
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Adrenaline*—avoid as α-adrenergic effects blocked, with consequential paradoxical hypotension and tachycardia.
- *Antidiabetics*—glycaemic control may be impaired.
- *Anti-epileptics*—may need to be increased to take account of the lowered seizure threshold.
- *Antihypertensives*—increased risk of hypotension.
- *CNS depressants*—additive sedative effect.
- *Levodopa and dopamine agonists*—effect antagonized by haloperidol.
- *Levomepromazine*—may be an additive hypotensive effect; increased risk of extrapyramidal symptoms.
- *Metoclopramide*—increased risk of extrapyramidal symptoms.
- *Opioids*—may be an additive hypotensive effect.
- *Trazodone*—may be an additive hypotensive effect.

Dose

When prescribing haloperidol, the SUBCUT dose should be lower than the corresponding PO dose (which undergoes significant first-pass metabolism). There should be a separate prescription for each route, ensuring that the same dose cannot be given PO or SUBCUT or by CSCI. A ratio of 3:2 is suggested (i.e. 3mg PO = 2mg SUBCUT).

Delirium

- Initial dose 1mg to 3mg PO OD to TDS, titrated as required to achieve the maintenance dose (range 1.5mg to 10mg daily). Dose may be adjusted in increments at 2- to 4-hourly intervals if agitation continues, up to a maximum dose of 10mg daily.
- Alternatively, 1mg to 3mg SUBCUT OD or via CSCI. Increase to usual maximum dose of 10mg SUBCUT daily or via CSCI. Dose may be adjusted in increments at 2- to 4-hourly intervals if agitation continues, up to a maximum dose of 10mg daily.
- In less severe cases, a lower starting dose (e.g. 0.5mg SUBCUT OD) may be more suitable.

Intractable hiccup
- Initial dose 1.5mg PO BD to TDS and adjust to response.
- Usual maintenance dose 1.5mg to 3mg PO ON, or 0.5mg to 1mg PO TDS.
- [+]Alternatively, 1.5mg to 3mg SUBCUT OD or via CSCI, and adjust to response.

Persistent aggression in dementia
(NB—oral solutions only licensed for this use)
- 0.5mg to 5mg PO as a single daily dose or in two divided doses.
- Adjustments to the dose may be made every 1–3 days.
- The need for continued treatment must be reassessed after no more than 6 weeks.

Psychosis
- Refer to the SmPC.

Restlessness and agitation in the elderly
- Initial dose 1.5mg to 3mg PO BD to TDS, titrated as required to achieve maintenance dose (range 1.5mg to 20mg PO daily).
- May be prescribed on a PRN basis (e.g. 1.5mg PO PRN, maximum BD to TDS).
- [+]Alternatively, 1.5mg to 3mg SUBCUT OD or via CSCI. Can increase to usual maximum dose of 10mg SUBCUT daily or via CSCI.
- [+]May be prescribed on a PRN basis (e.g. 0.5mg to 1.5mg SUBCUT PRN maximum TDS).

[+]*Nausea and vomiting in palliative care*
- Initial dose 0.5mg to 1.5mg SUBCUT OD or via CSCI. Increase to usual maximum of 10mg SUBCUT daily or via CSCI.
- Dose may be adjusted in increments at 2- to 4-hourly intervals if symptoms continue, up to a maximum dose of 10mg daily.
- Consider an alternative treatment if 10mg is ineffective (e.g. levomepromazine).
- PO route not usually appropriate, but 1.5mg to 3mg PO ON to BD can be used. Can be increased to 5mg PO ON to BD as necessary.

[+]*Terminal agitation*
- In mild to moderate cases, haloperidol 0.5mg to 1mg SUBCUT OD or via CSCI. Dose can be increased as necessary to a usual maximum dose of 10mg.
- In severe cases, 0.5mg to 2mg SUBCUT every 1–4 hours PRN and titrated to the lowest effective dose. A CSCI may be used to maintain symptoms.
- Consider an alternative treatment if 10mg is ineffective (e.g. midazolam ± levomepromazine).

Dose adjustments

Elderly
- Wherever possible, lower doses should be used. The elderly are more susceptible to adverse effects, particularly anticholinergic effects; there may be an increased risk of cognitive decline and dementia.

Hepatic/renal impairment

- In hepatic impairment, it is recommended to reduce the initial dose by 50% and adjust the dose with smaller increments and at longer intervals than in patients with normal function.
- In renal impairment, no specific guidance is available. Although <3% of a dose is excreted unchanged in the urine and metabolites are not expected to have significant activity, caution is advised in patients with severe renal impairment; there is a risk of back conversion of the reduced metabolite of haloperidol to haloperidol.

Additional information

- Injection must not be administered IV.
- Haloperidol is stated to be *chemically and physically* compatible under stated conditions with hyoscine butylbromide, midazolam, morphine hydrochloride, oxycodone, and tramadol. Under stated conditions, haloperidol is *physically* compatible with cyclizine, fentanyl, lorazepam, methadone, and metoclopramide. Haloperidol appears to show diluent and concentration-dependent compatibility with diamorphine, hydromorphone, and morphine sulfate.[2]

Pharmacology

The pharmacology of haloperidol has not as yet been fully elucidated. It is a butyrophenone antipsychotic agent which selectively acts via dopamine D_2 receptors. Haloperidol may antagonize σ_1 receptors, although the clinical significance of this remains to be determined (potential anti-nociceptive effect). It also has weak effects at α_1-adrenoreceptors and 5-HT_2 receptors. It reportedly has minimal effects on muscarinic and H_1 receptors. The metabolism of haloperidol is complex, with a variety of metabolites being formed (including weakly active metabolites). It is extensively metabolized, with only approximately 1% of the administered dose being excreted unchanged in the urine. Glucuronidation is the main metabolic pathway, accounting for 50–60% of the biotransformation of haloperidol. UGT2B7 is believed to be the main enzyme involved in glucuronidation (minor routes involve UGT1A4 and UGT1A9). Other routes of metabolism involve CYP2D6 and (at higher doses) CYP3A4, with a minor pathway involving CYP1A2.

References

1. Schrijver EJ, Verstraaten M, van de Ven PM, *et al*. Low dose oral haloperidol does not prolong QTc interval in older acutely hospitalised adults: a subanalysis of a randomised double-blind placebo-controlled study. *J Geriatr Cardiol*. 2018;**15**(6):401–7.
2. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Hydromorphone

Standard-release

Palladone® **(***CD2 POM***)**
Capsule: 1.3mg (*orange/clear*—56); 2.6mg (*red/clear*—56).
Injection (clear, colourless to pale yellow solution): 2mg/mL (5); 10mg/mL (5).

Modified-release

Palladone SR® **(***CD2 POM***)**
Capsule: 2mg (*yellow/clear*—56); 4mg (*pale blue/clear*—56); 8mg (*pink/clear*—56); 16mg (*brown/clear*—56); 24mg (*dark blue/clear*—56).

Indications

- Relief of severe cancer pain.

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care, although there may be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation). Nonetheless, the SmPC contraindicates hydromorphone for use in patients with:
  - acute abdomen
  - concurrent administration of MAOIs (including *linezolid*, *moclobemide*, *rasagiline*, *selegiline)* or within 2 weeks of discontinuation of their use
  - severe COPD
  - cor pulmonale
  - hepatic impairment (see ➔ *Dose adjustments*, p. 340)
  - paralytic ileus
  - significant respiratory depression with hypoxia or hypercapnia.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 339). Of the opioids, *morphine* is believed to carry the lowest risk. Treatment must be reviewed urgently if symptoms develop, hydromorphone should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of hydromorphone and benzodiazepines (or *zopiclone/zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution in the following instances:

- acute alcoholism
- Addison's disease (adrenocortical insufficiency)
- biliary or ureteric colic
- cholecystectomy
- COPD
- delirium tremens
- diseases of the biliary tract
- elderly patients (see *Dose adjustments*, p. 340)
- epilepsy
- head injury (risk of increased intracranial pressure)
- hepatic impairment (see above)
- history of alcohol and drug abuse
- hypotension with hypovolaemia
- hypothyroidism
- inflammatory or obstructive bowel disorders
- pancreatitis
- prostatic hypertrophy
- renal impairment (see *Dose adjustments*, p. 340)
- sleep apnoea (respiratory effects of opioids are more pronounced during sleep)
- toxic psychosis.

- Hydromorphone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

Adverse effects

Refer to the SmPC for a full list of adverse effects. Strong opioids tend to cause similar adverse effects, albeit to varying degrees.

- *Very common*: constipation; dizziness; nausea; somnolence.
- *Common*: abdominal pain; anxiety; reduced appetite; asthenia; confusion; dry mouth; headache; hyperhidrosis; injection site reactions; insomnia; pruritus; vomiting.
- *Uncommon*: agitation; depression; diarrhoea; dysgeusia; dyspnoea; euphoria; fatigue; hallucinations; hypotension (including postural

hypotension); increased LFTs; malaise; myoclonus (associated with toxicity); nightmares; paraesthesia; peripheral oedema; rash; sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence); tremor; urinary retention; visual disturbance.
- *Rare*: lethargy; respiratory depression; sedation; tachycardia.
- *Unknown*: anaphylaxis/hypersensitivity; convulsions; dyskinesia; dysphoria; flushing; hyperalgesia; miosis; paralytic ileus; tolerance; urticaria.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- The major route of metabolism is via glucuronidation through UGT1A3 and UGT2B7. CYP3A4 and CYP2C9 appear to have a minor role in the metabolism of hydromorphone. To date, no clinically significant pharmacokinetic interactions have been reported.
- *Cannabidiol*—theoretical interaction as cannabidiol is a UGT2B7 inhibitor.

Pharmacodynamic
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 337.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing affect, with consequential adverse effects, such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of hydromorphone may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOI*—risk of CNS excitation or depression.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 337.

Dose

Note that it is generally accepted that PRN doses may be given every 2–4 hours (some centres suggest a maximum daily limit of six doses, irrespective of indication). In the case of severe pain or end-of-life care, PRN doses may be given as frequently as every hour under specialist supervision.

The initial dose of hydromorphone depends upon the patient's previous opioid requirements. Refer to ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56 or information regarding opioid dose equivalences. Refer to ➔ Chapter 2, *Breakthrough cancer pain*, p. 54 for guidance relating to BTcP.

Oral

Standard-release

- For opioid-naïve patients, initial dose is 1.3mg PO every 4–6 hours PRN (or more frequently, as described above). The dose is then increased as necessary until a stable dose is attained. The patient should then be converted to modified-release formulation.

Modified-release

- Patients should ideally be titrated using *Palladone®* before commencing *Palladone SR®*.
- If necessary, for opioid-naïve patients, the initial dose is 2mg PO BD. The dose can then be titrated as necessary.

Subcutaneous

- Initial dose in opioid-naïve patients is 1mg to 2mg via CSCI over 24 hours and increased as necessary.

Dose adjustments

Elderly

- No specific guidance available, although lower starting doses in opioid-naïve patients may be preferable. Dose requirements should be individually titrated.

Hepatic/renal impairment

- The SmPC contraindicates the use of hydromorphone in patients with any degree of hepatic impairment. Despite this, hydromorphone is considered by some to be the opioid of choice in patients with hepatic impairment. The US SmPC states that patients with moderate hepatic impairment should be started at a lower dose and closely monitored during dose titration. There are no data in patients with severe hepatic impairment. The dose should be titrated carefully to the patient's need. Consider reducing the initial dose by 50% and the frequency of doses to 6- to 8-hourly in patients with moderate to severe hepatic impairment. Avoid the modified-release formulation in severe hepatic impairment.
- No specific guidance is available in the SmPC for patients with renal impairment and dose requirements should be individually titrated. For patients with CrCl 10 to 50mL/min, a dose reduction of 25% is suggested. For patients with CrCl <10mL/min, a dose reduction of 50% is suggested; consider reducing the frequency of administration to 6- to 8-hourly. Avoid the modified-release formulation in severe renal impairment.

Additional information

- If other analgesic measures are introduced—pharmacological or other alternatives, e.g. radiotherapy—the dose of hydromorphone may need to be reduced.
- Capsules can be swallowed whole, or opened and their contents sprinkled onto cold, soft food. The contents of the prolonged-release capsule (pellets) must not be chewed or broken, as this will lead to rapid release.

- There are concentration-dependent compatibility issues when admixing hydromorphone with cyclizine or dexamethasone.
- Hydromorphone is *chemically and physically* compatible under stated conditions with cyclizine, dexamethasone, glycopyrronium, haloperidol, hyoscine butylbromide, hyoscine hydrobromide, ketamine, levomepromazine, metoclopramide, midazolam, and ondansetron. Under stated conditions, hydromorphone is *physically* compatible with ketorolac. Hydromorphone shows concentration-dependent compatibility with dexamethasone.[2]

Pharmacology

Hydromorphone is a synthetic analogue of morphine, with analgesic activity at MORs. Oral bioavailability is variable (the SmPC quotes 32%), with a PO:SUBCUT equianalgesic ratio of between 2:1 and 5:1 (the SmPC quotes 3:1). Hydromorphone is extensively metabolized via glucuronidation, with >95% of the dose metabolized to hydromorphone-3-glucuronide. The metabolite can accumulate in renal impairment and lead to symptoms, such as nausea, and neuroexcitatory effects such as delirium and myoclonus.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
2. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Hyoscine butylbromide

Buscopan® (POM)
Tablet: 10mg (56).
Injection: 20mg/mL (10).
NB—hyoscine butylbromide tablets can be sold to the public for irritable bowel syndrome, provided a single dose of ≤20mg, a daily dose of ≤80mg, and a pack containing ≤240mg.

Indications

- Spasm of the genitourinary tract or GI tract (tablet).
- Irritable bowel syndrome (tablet).
- †Intestinal obstruction/smooth muscle spasm (e.g. bowel colic).[1]
- †Terminal secretions.[2]

Contraindications and cautions

- Note that for the management of terminal secretions, contraindications should be individually assessed.
- The SmPC states that hyoscine butylbromide should be avoided in patients with:
  - mechanical stenosis in the GI tract
  - megacolon
  - myasthenia gravis
  - narrow-angle glaucoma
  - paralytic ileus
  - prostatic enlargement with urinary retention
  - tachycardia (parenteral use only).
- The MHRA issued an alert in 2017, warning of fatalities after IV or IM administration of hyoscine butylbromide.[2,3] Adverse effects such as tachycardia and hypotension are more likely in patients with underlying cardiac disease. Parenteral use in patients with the following cardiac disorders should be closely monitored:
  - cardiac arrhythmias
  - congestive heart failure
  - coronary artery disease
  - hypertension.
- It possesses anticholinergic properties, so it should be used with caution in the following:
  - bladder outflow obstruction
  - diarrhoea (may be masking intestinal obstruction)
  - elderly (more susceptible to adverse effects)
  - GI reflux disease
  - hyperthyroidism
  - narrow-angle glaucoma (risk of elevation of intraocular pressure)
  - pyrexia (reduces sweating)
  - renal impairment (see ➲ *Dose adjustments*, p. 344)
  - ulcerative colitis.
- Hyoscine butylbromide may affect vision or cause dizziness; patients should be advised not to drive (or operate machinery) if affected. Refer to ➲ Chapter 2, *Drugs and driving*, p. 41 for further information.

- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients. The risk of such effects is low with hyoscine butylbromide, as it does not readily cross the blood–brain barrier.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: accommodation disorders; constipation; dizziness; dry mouth; tachycardia.
- *Not known*: confusion; delirium; dyshidrosis; flushing; hypersensitivity (e.g. anaphylaxis, dyspnoea, erythema, pruritus, rash, urticaria); hypotension; injection site pain; urinary retention.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- No recognized pharmacokinetic interactions.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- The anticholinergic effect of hyoscine butylbromide can be additive with that of other drugs and *may* precipitate delirium or cognitive impairment in susceptible patients.
- *β_2-agonists*—increased risk of tachycardia.
- *Cyclizine*—increased risk of anticholinergic adverse effects.
- *Domperidone*—may inhibit prokinetic effect.
- *Metoclopramide*—may inhibit prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

Spasm of the genitourinary tract or GI tract

- 20mg PO QDS.
- [+]Alternatively, 10mg to 20mg SUBCUT injection initially, followed by 60mg via CSCI. Dose can be increased to a usual maximum of 120mg via CSCI over 24 hours; 20mg SUBCUT hourly PRN can be given as necessary.

Irritable bowel syndrome

- Initial dose 10mg PO TDS, increasing as necessary to 20mg PO QDS.

[+]*Intestinal obstruction/smooth muscle spasm/terminal secretions*

- Initial dose 20mg SUBCUT, repeated every hour as necessary, or 60mg via CSCI over 24 hours, with 20mg SUBCUT hourly PRN.
- Dose can be increased as necessary to a usual maximum of 120mg via CSCI over 24 hours.

- Larger doses (e.g. 240mg or greater) may be necessary to achieve adequate anti-secretory effects.

Dose adjustments

Elderly

- No specific guidance available. Use the lowest effective dose as the elderly may be more susceptible to adverse effects.

Hepatic/renal impairment

- No specific guidance available. However, given the fact that up to 50% of a dose is excreted renally, the lowest effective dose should be used in order to minimize adverse effects in patients with moderate to severe renal impairment.

Additional information

- Tablets may be crushed and added to water prior to administration if necessary.
- It is poorly absorbed orally, so the usefulness of this route of administration is questionable, apart from possible benefit in bowel colic.
- Hyoscine butylbromide administered SUBCUT may be useful for excessive sweating,[+] although other drugs may be more appropriate (e.g. glycopyrronium PO/SUBCUT, hyoscine hydrobromide transdermal, propantheline PO). The same doses as described for spasm of the genitourinary tract above can be used.
- Combination with octreotide *may* improve symptoms of bowel obstruction, although evidence is limited.
- Hyoscine butylbromide is *chemically and physically* compatible under stated conditions with diamorphine, haloperidol, hydromorphone, midazolam, morphine hydrochloride, morphine sulfate, oxycodone, and tramadol. Under stated conditions, hyoscine butylbromide is *physically* compatible with alfentanil, dexamethasone, metoclopramide, and ondansetron.[4]
- There may be concentration-dependent incompatibility when hyoscine butylbromide is combined with cyclizine.

Pharmacology

Hyoscine butylbromide is a quaternary ammonium antimuscarinic that inhibits the peripheral actions of acetylcholine. Following both oral and parenteral administration, hyoscine butylbromide concentrates in the tissues of the GI tract, liver, and kidneys. Although oral bioavailability is poor, the drug produces its effect because of its high tissue affinity. It is a quaternary ammonium compound, so it does not usually pass the blood–brain barrier; thus it is devoid of central activity such as drowsiness or a direct antiemetic effect.

References

1. Obita GP, Boland EG, Currow DC, Johnson MJ, Boland JW. Somatostatin analogues compared with placebo and other pharmacologic agents in the management of symptoms of inoperable malignant bowel obstruction: a systematic review. *J Pain Symptom Manage*. 2016;**52**(6):901–19.

2. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev*. 2008;**1**:CD005177.
3. Medicines and Healthcare products Regulatory Agency. Hyoscine butylbromide (Buscopan) injection: risk of serious adverse effects in patients with underlying cardiac disease. 2017. Available from: https://www.gov.uk/drug-safety-update/hyoscine-butylbromide-buscopan-injection-risk-of-serious-adverse-effects-in-patients-with-underlying-cardiac-disease. Accessed 12 July 2018.
4. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Hyoscine hydrobromide

Kwells® (P)
Tablet: 150 micrograms (12); 300 micrograms (12).

Joy-rides® (P)
Tablet: 150 micrograms.

Scopoderm® (POM)
Transdermal patch: 1.5mg (releasing 1mg over 72 hours).

Generic (POM)
Tablet: 300 micrograms (12).
Injection: 400 micrograms/mL (10); 600 micrograms/mL (10).

Indications

- Motion sickness (PO/transdermal).
- †Drooling/sialorrhoea.[1,2]
- †End-stage Parkinson's disease.[3]
- †Intestinal obstruction/smooth muscle spasm (e.g. bowel colic).[4]
- †Nausea and vomiting.[5]
- †Terminal secretions.[6]

Contraindications and cautions

- Note that for the management of terminal secretions, contraindications and cautions should be individually assessed.
- Contraindicated for use in patients with:
  - acute porphyria
  - angle-closure glaucoma
  - intestinal obstruction
  - megacolon
  - myasthenia gravis
  - paralytic ileus
  - prostatic enlargement
  - tachycardia.
- Product SmPCs state use with caution in the following circumstances:
  - bladder outflow obstruction
  - cardiac arrhythmias
  - congestive heart failure
  - diarrhoea (may be masking intestinal obstruction)
  - Down's syndrome
  - elderly patients (see ➔ *Dose adjustments*, p. 348)
  - epilepsy (increased risk of seizures)
  - GI reflux disease
  - hepatic impairment
  - hypertension
  - hyperthyroidism (risk of tachycardia)
  - pyrexia (reduces sweating)
  - renal impairment
  - ulcerative colitis
  - urinary retention.

- If a patient's condition indicates that there might be raised intraocular pressure, the SmPC for *Scopoderm*® states that the patch can only be applied after an ophthalmological examination.
- Idiosyncratic reactions may occur with ordinary therapeutic doses of hyoscine hydrobromide (e.g. agitation, hallucinations).
- Care should be taken after removal of the transdermal patch, as adverse effects may persist for up to 24 hours or longer.
- Discontinuation of the patch after several days' use can precipitate withdrawal effects, including balance disturbances, dizziness, headache, nausea, and vomiting.
- Remove the transdermal patch prior to MRI due to risk of burns.
- Hyoscine hydrobromide may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.
- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency of adverse effects is not stated, but reported adverse effects include:

- agitation (paradoxical); amnesia; bradycardia (transient and with low doses); confusion; delirium; dizziness (*very common* for *Scopoderm*®); drowsiness (*very common* for *Scopoderm*®); dry mouth (*very common* for *Scopoderm*®); dyshidrosis; eyelid irritation (*common* for *Scopoderm*®); hallucinations; headache; hypersensitivity reactions (anaphylaxis, dyspnoea, eryrthema, pruritus, rash, urticaria); inhibition of sweating (risk of hyperthermia in hot weather or pyrexia); micturition difficulty; NMS; seizures (excessive doses); skin irritation (*common* for *Scopoderm*®); tachycardia (with higher doses); visual disturbances (e.g. angle-closure glaucoma, blurred vision, pupillary dilation) (blurred vision *very common* for *Scopoderm*®).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- No recognized pharmacokinetic interactions.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- The central anticholinergic effect of hyoscine hydrobromide will be additive with that of other drugs, which can precipitate delirium or cognitive impairment in susceptible patients.
- *Donepezil*—effect may be antagonized.
- β_2*-agonists*—increased risk of tachycardia.
- *Cyclizine*—increased risk of anticholinergic adverse effects.
- *Domperidone*—may inhibit prokinetic effect.

- *Galantamine*—effect may be antagonized.
- *Metoclopramide*—may inhibit prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *Rivastigmine*—effect may be antagonized.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

+Drooling/sialorrhoea

- 1mg every 72 hours via transdermal patch. Up to *four* patches may be used if necessary.
- It may be more appropriate to use alternative treatments (e.g. amitriptyline, glycopyrronium, propantheline) due to the development of skin irritation from the transdermal formulation.

+End-stage Parkinson's disease

- Note other treatment options may be preferable (e.g. rotigotine transdermal patches).
- A single case study reported successful treatment of severe tremors.
- Initial dose 1.2mg via CSCI over 24 hours, and adjust empirically.

+Intestinal obstruction/smooth muscle spasm

- Note other treatment options may be preferable
- Initial dose 400 micrograms SUBCUT injection, followed by 600 micrograms to 800 micrograms via CSCI over 24 hours. Consider 400 micrograms SUBCUT hourly PRN. Dose can be increased to usual maximum of 2.4mg via CSCI over 24 hours.

+Nausea and vomiting

- Note other treatment options may be preferable (e.g. levomepromazine).
- 1mg every 72 hours via transdermal patch. Up to *four* patches may be used if necessary.
- Alternatively, 300 micrograms PO up to QDS can be tried.
- Via CSCI, initially 400 micrograms over 24 hours, increased as necessary up to 1.2mg.

+Terminal secretions

- Initial dose 400 micrograms SUBCUT hourly PRN. Consider 1.2mg via CSCI over 24 hours.
- If necessary, the dose can be increased to 2.4mg over 24 hours.
- Alternatively, if other options are unavailable, consider:
  - 300 micrograms PO up to QDS
  - 1mg every 72 hours via transdermal patch; up to *four* patches may be used if necessary.

Dose adjustments

Elderly

- No specific guidance available. Use the lowest effective dose, as the elderly may be more susceptible to adverse effects, particularly anticholinergic effects. The patient may be at increased risk of cognitive decline and dementia.

Hepatic/renal impairment

- More suitable alternatives are suggested for use in patients with hepatic and renal impairment, given the central sedative effects of hyoscine hydrobromide.

Additional information

- *Kwells*® and *Joy-rides*® can be sucked, chewed, or swallowed.
- *Scopoderm*® patches are reservoir patches and should not be cut in an attempt to reduce the dose. They are best applied to hairless skin, as located behind the ear.
- The transdermal patch should be placed in the post-auricular area where the skin is thin and absorption is superior.
- Effects may persist for up to 24 hours or longer after removal of the patch.
- Hyoscine hydrobromide is *chemically and physically* compatible under stated conditions with diamorphine, hydromorphone, and oxycodone. Under stated conditions, hyoscine hydrobromide is *physically* compatible with dexamethasone, fentanyl, methadone, and morphine sulfate.[7]

Pharmacology

Hyoscine hydrobromide is an anticholinergic drug which blocks the action of acetylcholine at post-ganglionic parasympathetic sites, including smooth muscle, secretory glands, and CNS sites. It effectively reduces secretions (bowel, salivary, and bronchial), has a direct antiemetic effect (unlike glycopyrronium and hyoscine butylbromide), and reduces sweating. It may cause amnesia and unlike glycopyrronium, it is more likely to cause bradycardia, rather than tachycardia. It is extensively metabolized, although the exact details are unknown.

References

1. Mato A, Limeres J, Tomás I, *et al*. Management of drooling in disabled patients with scopolamine patches. *Br J Clin Pharmacol*. 2010;**69**(6):684–8.
2. McGeachan AJ, Hobson EV, Al-Chalabi A, *et al*. A multicentre evaluation of oropharyngeal secretion management practices in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;**18**(1–2):1–9.
3. Pérez LM, Farriols C, Puente V, Planas J, Ruiz I. The use of subcutaneous scopolamine as a palliative treatment in Parkinson's disease. *Palliat Med*. 2011;**25**(1):92–3.
4. Ripamonti C, Twycross R, Baines M, *et al*. Clinical-practice recommendations for the management of bowel obstruction in patients with end-stage cancer. *Support Care Cancer*. 2001;**9**(4):223–33.
5. LeGrand SB, Walsh D. Scopolamine for cancer-related nausea and vomiting. *J Pain Symptom Manage*. 2010;**40**(1):136–41.
6. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev*. 2008;**1**:CD005177.
7. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Ibandronic acid (ibandronate)

Generic (POM)

Tablet: 50mg (28).
Injection (concentrate): 2mg/2mL vial; 6mg/6mL vial.

Indications

- Prevention of skeletal events in patients with breast cancer and bone metastases.
- Treatment of tumour-induced hypercalcaemia (*injection only*).
- Treatment of post-menopausal osteoporosis (*not discussed*).

Contraindications and cautions

- Ibandronic acid is contraindicated in the following situations:
  - abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia (*tablet*)
  - inability to stand or sit upright for at least 60 minutes (*tablet*)
  - hypocalcaemia.
- Osteonecrosis of the jaw has been reported rarely in patients receiving ibandronic acid. Cancer patients are more likely to be at risk of osteonecrosis as a result of their disease, cancer therapies, and blood dyscrasias. Dental examination and appropriate preventative dentistry are recommended prior to treatment. Dental surgery should be avoided during this treatment. Patients should maintain good oral hygiene while receiving long-term ibandronic acid, receive routine dental check-ups, and be encouraged to report any oral symptoms.
- Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Patients should be advised to report any ear pain, ear infection, or discharge from the ear.
- Atypical femoral fractures have been rarely reported in patients receiving long-term bisphosphonate treatment. Patients should be advised to report any new thigh, hip, or groin pain.
- Use with caution in patients with renal impairment (see ➔ *Dose adjustments*, p. 351).
- Assess the need for calcium and vitamin D supplements in patients receiving ibandronic acid other than for hypercalcaemia.
- Oral ibandronic acid may cause local irritation of the upper GI mucosa. Use with caution in patients with upper GI problems (e.g. Barrett's oesophagus, dysphagia, gastritis, duodenitis, peptic ulcers). Patients should not lie down for 60 minutes after taking. See also ➔ *Drug interactions*, p. 351.

Adverse effects

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported with bisphosphonate use. Time to onset varies from one day to several months after initiation of treatment, but symptoms should improve upon discontinuation. Some patients will develop the same symptoms upon subsequent treatment with ibandronic acid or another bisphosphonate.

Refer to the SmPC for a full list of adverse effects.

- *Common*: arthralgia; asthenia; bone pain; bundle branch block; cataract; diarrhoea; dizziness; dysgeusia; dyspepsia; ecchymosis; increased GGT; hypocalcaemia; influenza-like illness; headache; myalgia; nausea (*PO route*); osteoarthritis; peripheral oedema; oesophagitis (*PO route*); pharyngitis; pyrexia; vomiting.
- *Uncommon*: alopecia; increased ALP; amnesia; anaemia; anxiety; blood dyscrasia; candidosis; cheilitis; cholelithiasis; cystitis; deafness; dry mouth (*PO route*); duodenal ulcer (*PO route*); dysphagia; gastritis; hypertonia; hypophosphataemia; hypothermia; injection site pain; lung oedema; migraine; mouth ulceration; myocardial ischaemia; paraesthesia; parosmia; pelvic pain; pruritus (*PO route*); rash; sleep disorder; stridor; urinary retention.
- *Rare*: atypical femoral fractures; ocular inflammation.
- *Very rare*: erythema multiforme; hypersensitivity reactions (anaphylaxis; angioedema; bronchospasm); osteonecrosis of the external auditory canal; osteonecrosis of the jaw; Stevens–Johnson syndrome.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None known.

Pharmacodynamic

- *Aminoglycosides*—may have additive hypocalcaemic effect.
- *Calcitonin*—likely additive Ca^{2+}-lowering effect.
- *NSAIDs*—may increase risk of GI irritation.

Dose

Tumour-induced hypercalcaemia

- Ensure adequate hydration prior to administration.
- Corrected serum Ca^{2+} <3.0mmol/L, 2mg by IVI as a single dose.
- Corrected serum Ca^{2+} >3.0mmol/L, 4mg by IVI as a single dose.
- Dilute appropriate dose in 500mL of NaCl or GLU and give over 2 hours.

Prevention of skeletal events

- 50mg PO OD.
- Alternatively, 6mg by IVI every 3–4 weeks. Administer in 100mL of NaCl or GLU over 15 minutes (for patients with CrCl >50mL/min).
- Note that calcium 500mg and vitamin D 400 units should also be taken daily.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- No dose adjustments are necessary for patients with hepatic impairment.

- Ibandronic acid is renally excreted; the manufacturer does not make a specific recommendation for dose adjustment when prescribing for hypercalcaemia (note that for treatment of hypercalcaemia, the SmPC does suggest an infusion rate of at least 2 hours). However, adjustments must be made when treating skeletal events:
  - CrCl 30–50mL/min:
    - reduce IV dose to 4mg and infuse over at least 1 hour in 500mL of NaCl or GLU.
    - reduce PO dose to 50mg PO ALT DIE
  - CrCl <30mL/min:
    - reduce dose to 2mg and infuse over at least 1 hour in 500mL of NaCl or GLU
    - reduce PO dose to 50mg PO *weekly*.

Additional information

- Corrected serum Ca^{2+} (mmol/L) = actual serum Ca^{2+} + [(40 − serum albumin g/L) × 0.02].
- In the treatment of hypercalcaemia, serum Ca^{2+} levels should not be measured until 5–7 days post-dose. Ca^{2+} levels start to fall after 48 hours, with a median time to normalization of 4–7 days and normalization in 80% of patients within 7 days. Seek specialist advice should the corrected serum Ca^{2+} concentration not return to normal after 7–10 days; a second dose of ibandronic acid can be given 7–10 days after the initial dose in such patients.
- The onset of treatment effect for skeletal-related events is 2–3 months.
- Relief from bone pain may occur within 14 days, although it may be up to 3 months before maximum effect is seen.

Pharmacology

Ibandronic acid is a bisphosphonate that inhibits osteoclast activity, which, in turn, reduces bone resorption and turnover. It is excreted unchanged by the kidney.

Ibuprofen

Standard-release

Brufen® (POM)
Tablet: 400mg (60); 600mg (60).
Effervescent granules: 600mg (20) (*contains 9mmol Na^+ per sachet*).
Syrup: 100mg/5mL (500mL).

Generic **(*POM*)**
Tablet: 600mg (84).
Oral suspension: 20mg/mL (500mL).

Generic (P)
Tablet: 200mg (24; 48; 96); 400mg (16; 24; 48; 96).
Oral suspension: 20mg/mL (150mL; 200mL).

Modified-release

Brufen Retard® (POM)
Tablet: 800mg (56).
NB—ibuprofen is also available OTC in a variety of formulations (e.g. tablets, caplets, capsules, creams, foams, gels) and strengths.

Indications

- Mild to moderate pain.
- Inflammatory conditions (e.g. rheumatoid and other musculoskeletal disorders).
- Fever.
- ✝Pain associated with cancer.[1,2]

Contraindications and cautions

- Contraindicated for use in patients with:
  - conditions involving an increased tendency to bleeding
  - history of, or active, recurrent peptic ulceration or GI haemorrhage
  - history of GI bleeding or perforation related to previous NSAID therapy
  - hypersensitivity reactions (e.g. asthma, nasal polyps, rhinitis) to aspirin or other NSAIDs
  - severe heart failure.
- Risks of CV and GI toxicities may increase with dose (>1200mg/day) and duration of exposure. Use the minimum effective dose for the shortest duration necessary in order to reduce the risk of cardiac and GI events. Treatment should be reviewed *2 weeks* after initiation and the continued need for treatment should be regularly reassessed. In the absence of benefit, other options should be considered.
- Elderly patients are more at risk of developing adverse effects.
- Avoid co-administration with low-dose aspirin.
  - Aspirin irreversibly inhibits platelet COX-1, but the plasma half-life of aspirin is short, being approximately 15–20 minutes. Ibuprofen, with a half-life of up to 4 hours, binds to sites that are in close proximity to the aspirin binding site on platelet COX-1. Upon concurrent administration, the ensuing pharmacodynamic interaction prevents

aspirin from irreversibly acetylating COX-1 and it is unlikely there will be any aspirin remaining in the circulation once ibuprofen has been released from the binding site. Notwithstanding the potential increased risk of GI toxicity, ibuprofen reduces the beneficial antiplatelet action of aspirin.
  - Ibuprofen only binds reversibly to the COX-1 enzyme in the platelet. Due to the transient nature of binding, ibuprofen does not have a meaningful antiplatelet effect.
- Use with caution in the following circumstances:
  - asthma (risk of bronchospasm)
  - atopy (risk of angioedema, bronchospasm, or urticaria)
  - concurrent use of diuretics, ACE-Is, ARBs, corticosteroids, and NSAIDs (see ➔ *Drug interactions*, p. 355)
  - congestive heart failure and/or left ventricular dysfunction
  - diabetes mellitus (risk factor for CV adverse effects)
  - established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease need careful consideration due to the increased risk of thrombotic events (especially at doses >1200mg/day)
  - hepatic impairment
  - hyperlipidaemia
  - hypertension (particularly uncontrolled)
  - recovery from surgery
  - renal impairment
  - chronic rhinitis (risk of angioedema, bronchospasm, or urticaria)
  - smoking (higher risk of CV and GI toxicity)
  - SLE (risk of aseptic meningitis).
- Patients taking long-term therapy need regular monitoring of renal and liver function.
- Abnormal LFTs can occur; discontinue NSAID if this persists.
- Patients known to be CYP2C9 poor metabolizers should be treated with caution because there is an increased risk of adverse effects; similarly, drugs that inhibit CYP2C9 should be used with caution (see ➔ *Drug interactions*, p. 355). In both cases, the prescriber should consider reducing the dose to half the lowest recommended dose.
- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk within the first month of treatment. Acute generalized exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with ibuprofen must not be restarted.
- It may be wise to *avoid ibuprofen* in patients with *varicella infection* due to the risk of severe skin infections and soft tissue complications that have been reported in exceptional cases.
- Ibuprofen may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Consider co-prescription of misoprostol, PPI, or H_2 antagonist (usually reserved if PPI not possible) if at high risk of NSAID-induced GI toxicity,

e.g. long-term NSAID therapy, concurrent use of drugs that increase the risk of GI toxicity (see ➔ *Drug interactions*).
- Refer to ➔ Chapter 2, *Selection of an NSAID, p. 49* for further information about selecting an NSAID.
- Ibuprofen may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Common*: constipation; diarrhoea; dizziness; dyspepsia; fatigue; haematemesis; headache; GI haemorrhage; melaena; nausea; rash; vomiting.
- *Uncommon*: abnormal LFTs; angioedema; anxiety; asthma; bronchospasm; dyspnoea; gastritis; gastroduodenal ulcer; GI perforation and bleeding; impaired hearing; hepatitis; insomnia; jaundice; mouth ulceration; nephrotoxicity (e.g. nephrotic syndrome, renal failure); paraesthesia; photosensitivity reaction; pruritus; somnolence; tinnitus; urticaria; vertigo; visual impairment.
- *Rare*: anaphylaxis; aseptic meningitis (possibly linked to underlying SLE); blood dyscrasias (e.g. agranulocytosis, aplastic anaemia, haemolytic anaemia, leucopenia, neutropenia, thrombocytopenia); confusional state; depression; oedema; optic neuritis; toxic optic neuropathy.
- *Very rare*: severe forms of skin reactions (e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Ibuprofen is metabolized mainly by CYP2C9; other pathways involve CYP2C8, CYP2C19, CYP3A4, and several uridine diphosphate glucuronosyltransferases (UGTs) (e.g. UGT1A3, UGT2B7, UGT2B17). Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Digoxin*—monitoring of serum digoxin is recommended.
- *Fluconazole*—plasma concentration of ibuprofen may be increased (consider a dose reduction).
- *Methotrexate*—reduced excretion of methotrexate.
- *Miconazole*—may increase the effectiveness of ibuprofen (consider a dose reduction).
- *Warfarin*—possible increased risk of bleeding through inhibition of warfarin metabolism (5–11% of Caucasians have a variant of CYP2C9, requiring lower maintenance doses of warfarin; combination with ibuprofen may further reduce warfarin metabolism).

Pharmacodynamic

- *ACE-Is/ARBs*—risk of AKI.
- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—reduced antihypertensive effect.
- *Antiplatelet drugs*—increased risk of bleeding.
- *Aspirin (low dose)*—concomitant use should be avoided (see ➔ *Contraindications and cautions*, p. 353).
- *Corticosteroids*—increased risk of GI toxicity.
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Digoxin*—NSAIDs may exacerbate cardiac failure.
- *Diuretics*—reduced diuretic effect; risk of AKI.
- *Quinolone antibiotics*—risk of convulsions.
- *SSRIs*—increased risk of GI bleeding.
- *Trimethoprim*—increased risk of hyperkalaemia.

Dose

Ensure gastroprotection (e.g. a PPI) is prescribed for patients at risk of NSAID-induced GI toxicity.

Standard-release

- Initial dose 400mg PO TDS.
- The dose can be increased, if necessary, to a maximum of 600mg PO QDS. Note the risks of CV and GI toxicities may increase with doses >1200mg/day.

Modified-release

Brufen Retard®

- Initial dose two tablets (1600mg) PO OD, preferably in early evening, several hours before going to bed.
- Can be increased to three tablets (2400mg) PO daily in two divided doses.

Dose adjustments

Elderly

- Usual adult doses recommended. Note that the elderly are particularly susceptible to adverse effects. Use the lowest effective dose and for the shortest duration possible.

Hepatic/renal impairment

- No specific dosage modifications are available for patients with hepatic impairment. However, NSAIDs should be used cautiously in patients with mild to moderate hepatic impairment due to the increased risk of adverse effects such as variceal haemorrhage, impaired renal function, and diuretic-resistant ascites. The lowest effective dose should be used for the shortest time permissible and regular monitoring of liver and/or renal function is advisable. Ibuprofen is contraindicated for use in patients with severe hepatic impairment.
- No specific guidance is available for use in mild to moderate renal impairment. The elderly and those with pre-existing impaired renal function, cardiac failure, or hepatic impairment (due to reliance on the compensatory actions of prostaglandins on renal perfusion) are

at greatest risk of renal toxicity. Use the lowest effective dose and for the shortest duration possible. Close monitoring of renal function is recommended. Use of ibuprofen in severe renal impairment, however, is contraindicated.

Additional information

- Ibuprofen at doses <1200mg/day appears not to increase the risk of thrombotic events.
- It is considered to be one of the safest NSAIDs in terms of GI toxicity, especially at doses <1200mg/day.

Pharmacology

Ibuprofen is an NSAID that possesses anti-inflammatory, analgesic, and antipyretic activity. It exists as a racemic mixture of R- and S-enantiomers, with S-ibuprofen being largely responsible for its pharmacologic activity. Its mode of action, like that of other NSAIDs, is not completely understood but may be related to inhibition of COX-1 and COX-2. Ibuprofen is well absorbed orally and is rapidly metabolized and eliminated in the urine.

References

1. Derry S, Wiffen PJ, Moore RA, *et al*. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database Syst Rev*. 2017;**7**:CD012638.
2. Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. *Br J Anaesth*. 2019;**123**(2):e412–23.

Insulin

Product information is at the end of this monograph.

Indications

- Diabetes mellitus.

Contraindications and cautions

- Refer to individual product SmPCs for specific advice.
- For SUBCUT use only, unless specifically stated otherwise in the SmPC (see ➔ *Product information*, p. 359).
- Use with caution in the following:
  - concurrent use of drugs known to affect glycaemic control (see ➔ *Drug interactions*)
  - elderly patients (see ➔ *Dose adjustments*, p. 359)
  - renal impairment (see ➔ *Dose adjustments*)
  - severe hepatic impairment (see ➔ *Dose adjustments*)
  - systemic illness (dose increase may be necessary).
- The risk of reduced warning symptoms of hypoglycaemia is increased in the following circumstances:
  - after transfer from animal insulin to human insulin
  - autonomic neuropathy
  - depression (particularly if receiving an SSRI—see ➔ *Drug interactions*)
  - elderly
  - frequent episodes of hypoglycaemia
  - long history of diabetes.
- Refer to ➔ Chapter 2, *Diabetes in palliative care*, p. 80 for further information relating to diabetes management in palliative care.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: hypoglycaemia (also depends on other factors).
- *Uncommon*: injection site reactions (generally minor, e.g. redness, pain, itching, inflammation); lipodystrophy (rotation of injection site will reduce the risk); oedema (may cause Na^+ retention; usually transitory during initiation); peripheral neuropathy; retinopathy (temporary deterioration associated with abrupt improvement in glycaemic control can occur; long-term improved glycaemic control can result in reduced risk of diabetic retinopathy progression); urticaria; visual disturbances (usually temporary due to marked improvement in glycaemic control and associated altered lens properties).
- *Very rare*: hypersensitivity reactions (e.g. anaphylaxis, dyspnoea, skin rash).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None recognized.

Pharmacodynamic

- *ACE-Is*—increased risk of hypoglycaemia.
- *Antidepressants*—glycaemic control may be affected; dose adjustments may be necessary.
- *Antipsychotics*—glycaemic control may be affected; dose adjustments may be necessary.
- *β_2-agonists*—hypoglycaemic effect may be antagonized.
- *Corticosteroids*—hypoglycaemic effect antagonized.
- *Diuretics*—hypoglycaemic effect may be antagonized.
- *MAOIs*—glycaemic control may be affected; dose adjustments may be necessary.
- *Octreotide*—can affect glucose metabolism; dose adjustments may be necessary.
- *SSRIs*—increased risk of hypoglycaemia and impaired awareness of hypoglycaemia.

Dose

- In all cases, the dose is individual and determined by the needs of the patient. For specific information, refer to the SmPC.
- The duration of action of any insulin is dependent on dose, site of injection, blood supply, temperature, and physical activity.
- Also see *Product information*.

Dose adjustments

Elderly

- In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Hepatic/renal impairment

- In both cases, glucose monitoring will need to be intensified.
- In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism. Note, however, that in patients with chronic hepatic impairment, insulin requirements may increase due to a rise in insulin resistance.
- In patients with renal impairment, insulin requirements may be diminished due to reduced insulin metabolism.

Additional information

- During the early stages of palliative care, diabetes should be managed conventionally. Typically, aim for a pre-meal glucose concentration of 4 to 7mmol/L, or 9mmol/L after a meal.
- As disease progresses and prognosis becomes short term, the importance of treatment shifts to preventing symptomatic hyperglycaemia and hypoglycaemia. Fasting blood glucose should be maintained between 8mmol/L and 15mmol/L.

Product information

Biphasic insulin aspart
NovoMix® 30 (POM)

Biphasic insulin aspart (recombinant human insulin analogue), 100 units/mL (as 30 units/mL insulin aspart, 70 units/mL insulin aspart protamine).
Injection: 5 × 3mL *Penfill*® cartridge for *Novopen*® devices.
Injection: 5 × 3mL prefilled disposable *FlexPen*® injection devices; range 1–60 units, allowing 1 unit dosage adjustment).

- Biphasic insulin aspart is a suspension of human insulin aspart complexed with protamine sulfate, combined with insulin aspart. The net effect is a formulation with an immediate effect, followed by a more sustained action. Onset of action is within 10–20 minutes, with a maximum effect within 1–4 hours; the duration of effect is up to 24 hours.
- *NovoMix® 30* has a faster onset of action than biphasic human insulin and should generally be given up to 10 minutes before a meal (or soon after, if necessary). It may have a more pronounced glucose-lowering effect up to 6 hours after injection, which the patient may have to compensate for, through dose adjustments or food intake.
- Biphasic insulin aspart is given SUBCUT. Doses above 30 units OD should be divided into two equal doses.
- In patients with Type 2 diabetes, biphasic insulin aspart can be combined with oral antidiabetic drugs. The usual starting dose is 6 units at breakfast and 6 units with the evening meal. It can also be initiated as 12 units with the evening meal.
- If BD dosing results in recurrent daytime hypoglycaemic episodes, the morning dose can be split into morning and lunchtime doses (i.e. TDS regime).
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- When in use, or if carried as a spare, *Penfill*® cartridges and *FlexPen*® injection devices can be kept at room temperature (but below 30°C) and be protected from light, and must be discarded after 4 weeks. They must *not* be stored in a refrigerator (2–8°C) once used or carried as a spare.

Biphasic insulin lispro
Humalog® Mix25 (POM)
Biphasic insulin lispro (recombinant human insulin analogue), 25% insulin lispro, 75% insulin lispro protamine, 100 units/mL.
Injection: 1000 units/10mL vial.
Injection: 5 × 3mL cartridge for *Autopen® Classic or HumaPen®* devices.
Injection: 5 × 3mL prefilled disposable *KwikPen*® injection devices; range 1–60 units, allowing 1 unit dosage adjustment.
Humalog® Mix50 (POM)
Biphasic insulin lispro (recombinant human insulin analogue), 50% insulin lispro, 50% insulin lispro protamine, 100 units/mL.
Injection: 5 × 3mL cartridge for *Autopen® Classic or HumaPen®* devices.
Injection: 5 × 3mL prefilled disposable *KwikPen*® injection devices; range 1–60 units, allowing 1 unit dosage adjustment.

- Biphasic insulin lispro is a suspension of insulin lispro complexed with protamine sulfate, combined with insulin lispro. The net effect is a formulation with an immediate effect, followed by a more sustained

action. Onset of action is within 15 minutes, with a maximum effect within 1–2 hours; the duration of effect is between 2 and 5 hours.
- *Humalog®* preparations have a fast onset of action and should generally be given within 15 minutes of a meal or snack containing carbohydrates.
- Before use, *Humalog®* preparations must be stored in a refrigerator (2–8°C) and must not be frozen.
- When in use or if carried as a spare:
  - cartridges and *KwikPen®* injection devices must *not* be stored in a refrigerator (2–8°C)
  - vials *can* be stored in a refrigerator (2–8°C)
  - all formulations must not be stored above 30°C
  - all products must be discarded after 4 weeks (28 days).

Biphasic isophane insulin

Humulin® M3 (POM)

Biphasic isophane insulin (human), 30% soluble, 70% isophane, 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL cartridge for most *Autopen® Classic* or *HumaPen®* devices.

Injection: 5 × 3mL prefilled disposable *KwikPen®* injection devices (range 1–60 units, allowing 1 unit dosage adjustment).

Insuman® Comb 15 (POM)

Biphasic isophane insulin (human), 15% soluble, 85% isophane, 100 units/mL.

Injection: 5 × 3mL cartridge for *ClikSTAR®*, *Tactipen®*, *Autopen 24®*, *AllStar®*, and *AllStar® PRO* injection devices.

Insuman® Comb 25 (POM)

Biphasic isophane insulin (human), 25% soluble, 75% isophane, 100 units/mL.

Injection: 5mL vial.

Injection: 5 × 3mL cartridge for *ClikSTAR®*, *Tactipen®*, *Autopen 24®*, *AllStar®*, and *AllStar® PRO* injection devices.

Injection: 5 × 3mL prefilled disposable *SoloStar®* injection devices; range 1–80 units, allowing 1 unit dosage adjustment.

Insuman® Comb 50 (POM)

Biphasic isophane insulin (human), 50% soluble, 50% isophane, 100 units/mL.

Injection: 5 × 3mL cartridge for *ClikSTAR®*, *Tactipen®*, *Autopen 24®*, *AllStar®*, and *AllStar® PRO* injection devices.

Hypurin® Porcine 30/70 Mix (POM)

Biphasic isophane insulin (porcine, highly purified), 30% soluble, 70% isophane, 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL cartridge for *Autopen® Classic* device.

- Biphasic isophane insulin is a suspension of either porcine or human insulin complexed with protamine sulfate, combined with soluble insulin. The net effect is a formulation with an immediate effect, followed by a more sustained action. Onset of action is within 30 minutes, with a maximum effect within 2–8 hours; the duration of effect is up to 24 hours.
- An injection should be followed within 30 minutes by a meal or snack containing carbohydrates.

- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- When in use or if carried as a spare:
  - *Humulin® M3* formulations must not be stored above 30°C.
  - *Insuman®* and *Hypurin®* must not be stored above 25°C.
  - *Humulin® M3* cartridges and *KwikPen®* injection devices must *not* be stored in a refrigerator (2–8°C).
  - *Humulin® M3* vials *can* be stored in a refrigerator (2–8°C).
  - *Insuman® Comb 15* cartridges, *Insuman® Comb 25* cartridges or *SoloStar®* injection devices, and *Insuman® Comb 50* cartridges must *not* be stored in a refrigerator (2–8°C).
  - *Insuman® Comb 25* vials, once used, *can* be stored in a refrigerator (2–8°C).
  - *Hypurin® Porcine 30/70 Mix* cartridges or vials can be stored at up to 25°C.
  - All products must be discarded after 4 weeks (28 days).

Insulin aspart

Fiasp® (POM)

Insulin aspart, 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL *Penfill®* cartridge for use with Novo Nordisk reusable insulin pens and NovoFine Plus, NovoFine, or NovoTwist injection needles.

Injection: 5 × 3mL prefilled disposable *FlexTouch®* pen for use with NovoFine Plus, NovoFine, or NovoTwist injection needles; range 1–80 units, allowing 1 unit dosage.

- *Fiasp®* is recommended to be administered immediately prior to a meal (0–2 minutes) or up to 20 minutes after starting a meal. Inclusion of nicotinamide (vitamin B_3) in the formulation results in faster initial absorption of insulin, compared to *NovoRapid®*.
- Onset of action is within 5–10 minutes, with a maximum effect within 1–3 hours; the duration of effect is up to 3–5 hours.
- When in use or if carried as a spare:
  - all products must be stored below 30°C and protected from light
  - *Penfill®* cartridges must *not* be stored in a refrigerator (2–8°C)
  - *FlexTouch®* pens and vials *can* be stored in a refrigerator (2–8°C)
  - all products must be discarded after 4 weeks (28 days).

NovoRapid® (POM)

Insulin aspart, 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL *Penfill®* cartridge for *Novopen®* devices.

Injection: 5 × 3mL prefilled disposable *FlexPen®* injection devices; range 1–60 units, allowing 1 unit dosage.

Injection: 5 × 3mL prefilled disposable *FlexTouch®* injection devices; range 1–80 units, allowing 1 unit dosage.

Injection: 5 × 1.6mL *PumpCart®* cartridge for use with a suitable infusion pump.

- *NovoRapid*® is normally used in combination with intermediate- or long-acting insulin. It is usually administered by SUBCUT injection immediately before or shortly after meals. It can also be administered by continuous SUBCUT infusion, or by IV injection under specialist supervision.
- The onset of action following a SUBCUT injection is typically 10–20 minutes, with the maximum effect exerted between 1 and 3 hours. It has a duration of action of between 3 and 5 hours.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- *PumpCart*® cartridges can be used for a maximum of 7 days (below 37°C).
- Once used or if carried as a spare:
  - all products must be stored below 30°C and should be protected from light
  - vials, *Penfill*®, *and PumpCart*® cartridges must *not* be stored in a refrigerator (2–8°C)
  - *FlexPen*® and *FlexTouch*® injection devices *can* be stored in a refrigerator (2–8°C)
  - *PumpCart*® cartridges must be discarded after 2 weeks; other products must be discarded after 4 weeks (28 days).

Insulin degludec
Tresiba® (POM)
Insulin degludec, 100 units/mL.
Injection: 5 × 3mL *Penfill*® cartridge for *Novopen*® devices.
Injection: 5 × 3mL prefilled disposable *FlexTouch*® injection devices; range 1–80 units, allowing 1 unit dosage.
Insulin degludec, 200 units/mL.
Injection: 5 × 3mL prefilled disposable *FlexTouch*® injection devices; range 1–80 units, allowing 1 unit dosage.

- Is administered SUBCUT OD, at any time of the day, but preferably at the same time every day. If this is not possible, there is some degree of flexibility, but there must be a minimum of 8 hours between the doses.
- In Type 1 diabetes, insulin degludec must be combined with short-/rapid-acting insulin to cover mealtime insulin requirements.
- Following a SUBCUT injection, a depot is formed, from which insulin degludec is continuously and slowly absorbed into the circulation, leading to a flat and stable glucose-lowering effect over 24 hours.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- Once used or if carried as a spare:
  - all products must be stored below 30°C and should be protected from light
  - *Penfill*® cartridges must *not* be stored in a refrigerator (2–8°C)
  - *FlexTouch*® injection devices *can* be stored in a refrigerator (2–8°C)
  - all products should be discarded after 8 weeks (56 days).

Insulin detemir
Levemir® (POM)
Insulin detemir, 100 units/mL.
Injection: 5 × 3mL cartridge for *NovoPen*® devices.

Injection: 5 × 3mL prefilled disposable *FlexPen*® injection devices; range 1–60 units, allowing 1 unit dosage adjustment.
Injection: 5 × 3mL prefilled disposable *InnoLet*® injection devices; range 1–50 units, allowing 1 unit dosage adjustment.

- Insulin detemir is a long-acting human insulin analogue. It has a duration of action of 24 hours that closely resembles the basal insulin secretion of normal pancreatic β-cells. In patients with Type 1 diabetes, a short-/rapid-acting insulin taken with food will also be needed in order to reduce postprandial glucose elevations.
- A dose of insulin detemir 10 units SUBCUT ON will provide a basal insulin level and can be used if the patient is not eating.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- Once used or if carried as a spare:
  - all products must be stored below 30°C and should be protected from light
  - cartridges and *InnoLet*® injection devices must *not* be stored in a refrigerator (2–8°C)
  - *FlexPen*® injection devices *can* be stored in a refrigerator (2–8°C)
  - all products should be discarded after 6 weeks (42 days).

Insulin glargine
Lantus® *(POM)*
Insulin glargine, 100 units/mL.
Injection: 10mL vial.
Injection: 5 × 3mL cartridge for *ClikSTAR*®, *Tactipen*®, *Autopen 24*®, *AllStar*®, and *AllStar*® *PRO* injection device.
Injection: 5 × 3mL prefilled disposable *SoloStar*® injection devices (range 1–80 units, allowing 1 unit dosage adjustment).
Abasaglar® *(POM)*
Insulin glargine, 100 units/mL.
Injection: 5 × 3mL cartridge for *HumaPen*® injection device.
Injection: 5 × 3mL prefilled disposable *KwikPen*® injection devices.
Semglee® *(POM)*
Insulin glargine, 100 units/mL.
Injection: 5 × 3mL prefilled disposable injection devices.
Toujeo® *(POM)*
Insulin glargine, 300 units/mL.
Injection: 3 × 1.5mL prefilled disposable *SoloStar*® injection devices (range 1–80 units, allowing 1 unit dosage adjustment).
Injection: 3 × 3mL prefilled disposable *DoubleStar*® injection devices (range 2–160 units, allowing 2 unit dosage adjustment).

- Insulin glargine is a long-acting human insulin analogue. It has a duration of action of 24 hours that closely resembles the basal insulin secretion of normal pancreatic β-cells. In patients with Type 1 diabetes, a fast-acting insulin taken with food will also be needed in order to reduce postprandial glucose elevations.
- Is administered SUBCUT OD, at any time of the day, but preferably at the same time every day. Only the SmPC for *Toujeo*® allows some

flexibility, stating that if this is not possible, patients can administer up to 3 hours before or after their usual time of administration.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- Once used or if carried as a spare:
  - all products must be stored below 30°C, should be protected from light, and should be discarded after 4 weeks (28 days), *except SoloStar®* and *DoubleStar®* injection devices (after 6 weeks (42 days))
  - *Lantus®* cartridges and *SoloStar®* injection devices must *not* be stored in a refrigerator (2–8°C)
  - *Abasaglar®* cartridges and *KwikPen®* injection devices must *not* be stored in a refrigerator (2–8°C)
  - *Semglee®* injection devices must *not* be stored in a refrigerator (2–8°C)
  - *SoloStar®* and *DoubleStar®* injection devices must *not* be stored in a refrigerator (2–8°C).

Insulin glulisine
Apidra® (POM)
Insulin glulisine, 100 units/mL.
Injection: 10mL vial.
Injection: 5 × 3mL cartridge for *ClikSTAR®*, *Tactipen®*, *Autopen 24®*, *AllStar®*, and *AllStar® PRO* injection devices.
Injection: 5 × 3mL prefilled disposable *SoloStar®* injection devices (range 1–80 units, allowing 1 unit dosage adjustment).
- Insulin glulisine has a more rapid onset of action (about 10–20 minutes) and a shorter duration of action than regular human insulin. The maximum effect is exerted at 60 minutes and it has a duration of action of between 2 and 4 hours.
- It is usually administered by SUBCUT injection immediately before or shortly after meals. It can also be administered by CSCI, or by IVI under specialist supervision.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- Once used or if carried as a spare:
  - all products must be stored below 25°C (vials for IV use between 15°C and 25°C) and should be protected from light
  - cartridges and *SoloStar®* injection devices must *not* be stored in a refrigerator (2–8°C)
  - vials for IV use must be discarded after 48 hours; other products must be discarded after 4 weeks (28 days).

Insulin lispro
Humalog® (POM)
Insulin lispro, 100 units/mL.
Injection: 10mL vial.
Injection: 5 × 3mL cartridge for *Autopen® Classic or HumaPen®* devices.
Injection: 5 × 3mL prefilled disposable *KwikPen®* injection devices; range 1–60 units, allowing 1 unit dosage adjustment.
Insulin lispro, 200 units/mL.

Injection: 5 × 3mL prefilled disposable *KwikPen*® injection devices; range 1–60 units, allowing 1 unit dosage adjustment.

Insulin Lispro Sanofi (POM)

Insulin lispro, 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL cartridge for *Tactipen*®, *AllStar*®, and *AllStar*® *PRO* devices.

Injection: 5 × 3mL prefilled disposable injection devices; range 1–80 units, allowing 1 unit dosage adjustment.

- Insulin lispro has a rapid onset of action (about 15 minutes), with a maximum effect within 1–2 hours and a duration of activity of between 2 and 5 hours. It is usually administered SUBCUT immediately prior to, or within 15 minutes of, a meal. Insulin lispro can also be administered by CSCI, IVI, or IV injection under specialist supervision.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- Once used or if carried as a spare:
  - all products must be stored below 30°C and should be protected from light
  - *Humalog*® cartridges and *KwikPen*® injection devices must *not* be stored in a refrigerator (2–8°C)
  - *Insulin Lispro Sanofi* must *not* be stored in a refrigerator (2–8°C)
  - all products must be discarded after 4 weeks (28 days).

Isophane insulin

Humulin® I (POM)

Isophane insulin, 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL cartridge for *Autopen*® *Classic* or *HumaPen*® devices.

Injection: 5 × 3mL prefilled disposable *KwikPen*® injection devices; range 1–60 units, allowing 1unit dosage adjustment.

Insulatard® (POM)

Isophane insulin, 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL *Penfill*® cartridge for *Novopen*® device.

Injection: 5 × 3mL prefilled disposable *InnoLet*® injection devices; range 1–50 units, allowing 1unit dosage adjustment.

Insuman® Basal (POM)

Isophane insulin, 100 units/mL.

Injection: 5mL vial.

Injection: 5 × 3mL cartridge for *ClikSTAR*®, *OptiPen*® *Pro 1*, and *Autopen*® *24* injection devices.

Injection: 5 × 3mL prefilled disposable *Solostar*® injection devices; range 1–80 units, allowing 1 unit dosage adjustment.

Hypurin® Porcine Isophane (POM)

Isophane insulin (porcine, highly purified) 100 units/mL.

Injection: 10mL vial.

Injection: 5 × 3mL cartridge for *Autopen*® *Classic* device.

- Isophane insulin is a suspension of either porcine or human insulin complexed with protamine sulfate. Onset of action is within 90 minutes,

with a maximum effect within 4–12 hours; the duration of effect is up to 24 hours.
- It is administered by SUBCUT injection and may be used alone or mixed with fast-acting insulin.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- Once used or if carried as a spare:
  - all products should be protected from light
  - *Humulin® I* products, *Insulatard®* cartridges, and *InnoLet®* injection devices must be stored below 30°C. *Insulatard®* vials, *Insuman® Basal* products, and *Hypurin® Porcine Isophane* products must be stored below 25°C
  - the following products must *not* be stored in a refrigerator (2–8°C):
    - *Humulin® I* cartridges or *KwikPen®* injection devices
    - all *Insulatard®* products
    - *Insuman® Basal* cartridges or *Solostar®* injection devices
    - *Hypurin® Porcine Isophane* cartridges
  - should be discarded after 4 weeks (28 days), *except Insulatard®* products (after 6 weeks (42 days)).

Insulin—soluble
Actrapid® (POM)
Soluble insulin, 100 units/mL.
Injection: 10mL vial.
Humulin® S (POM)
Soluble insulin, 100 units/mL.
Injection: 10mL vial.
Injection: 5 × 3mL cartridge for *Autopen® Classic or HumaPen®* devices.
Hypurin® Porcine Neutral (POM)
Soluble insulin, 100 units/mL.
Injection: 10mL vial.
Injection: 5 × 3mL cartridge for *Autopen® Classic* device.
Insuman® Infusat (POM)
Soluble insulin, 100 units/mL.
Injection: 5 × 3.15mL cartridges for use with suitable insulin pumps.
Insuman® Rapid (POM)
Soluble insulin, 100 units/mL.
Injection: 5 × 3mL cartridge for *ClikSTAR®*, *OptiPen® Pro 1*, and *Autopen® 24* injection devices.
- Soluble insulin is fast-acting. Onset of action is within 30 minutes, with a maximum effect within 1–3 hours; the duration of effect is approximately 7–8 hours. It may be used in combination with intermediate- or long-acting insulins. An injection should be followed within 30 minutes by a meal or snack containing carbohydrates.
- Before use, all products must be stored in a refrigerator (2–8°C) and must not be frozen.
- Once used or if carried as a spare:
  - all products should be protected from light
  - *Humulin® S* products must be stored below 30°C

- *Actrapid®*, *Hypurin® Porcine Neutral*, and *Insuman® Rapid* products must be stored below 25°C
- the following products must *not* be stored in a refrigerator (2–8°C):
  - *Actrapid®*
  - *Humulin® S* cartridge
  - *Insuman® Rapid*
  - *Hypurin® Porcine Neutral* cartridge
- should be discarded after 4 weeks (28 days), *except Insuman® Infusat* (after 2 weeks (14 days)) *and Actrapid®* (after 6 weeks (42 days)).

Itraconazole ♡

Sporanox® (POM)
Capsule: 100mg (4; 15; 28).
Oral solution: 50mg/5mL (150mL).
Ampoules: 250mg/25mL (*solution for infusion*).

Generic (POM)
Capsule: 100mg (15; 60).
Oral solution: 50mg /5mL (150mL).

Indications

- Seek local microbiological advice before use.
- Oral and/or oesophageal candidosis in HIV-positive or other immunocompromised patients.
- Systemic fungal conditions when first-line systemic anti-fungal therapy is inappropriate or has proved ineffective.

Contraindications and cautions

- Co-administration of the following drugs is contraindicated:
  - CYP3A4-metabolized substrates that can prolong the QT interval (e.g. *domperidone*, *methadone*)
  - CYP3A4-metabolized HMG-CoA reductase inhibitors (e.g. *atorvastatin*, *simvastatin*)
  - midazolam (PO)—see ➔ *Drug interactions*, p. 370
  - naloxegol—see ➔ *Drug interactions*, p. 370.
- There is a *conditional* risk of QT prolongation/TdP (CYP3A4 inhibition—see above).
- Itraconazole has a dose-related negative inotropic effect and must not be administered to patients with, or with a history of, congestive heart failure, except for the treatment of life-threatening or other serious infections.
- Use with caution in patients with risk factors for congestive heart failure, including:
  - concurrent use of calcium channel blockers (see ➔ *Drug interactions*, p. 370)
  - COPD
  - high doses (of itraconazole) and prolonged treatment course
  - ischaemic or valvular disease
  - renal impairment.
- Hepatotoxicity has been reported. Warn the patient about the importance of reporting signs of hepatitis such as abdominal pain, anorexia, dark urine, fatigue, nausea, and vomiting. Treatment should be stopped immediately, and LFTs performed.
- Use with caution in patients with pre-existing liver disease; LFTs must be monitored closely if treatment is initiated.
- Absorption of itraconazole from capsules (*not oral liquid*) is reduced if gastric pH is raised (see ➔ *Drug interactions*, p. 370).
- Itraconazole is an inhibitor of CYP3A4. Many drugs metabolized by CYP3A4 can be affected. Similarly, CYP3A4 inducers may significantly reduce the effect of itraconazole (see ➔ *Drug interactions*, p. 370).

- Itraconazole may cause dizziness. Patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; nausea; rash.
- *Uncommon*: alopecia; constipation; diarrhoea; dizziness; dysgeusia; dyspepsia; flatulence; headache; hyperbilirubinaemia; hypersensitivity; increased liver enzymes; menstrual disorder; oedema; paraesthesia (discontinue if peripheral neuropathy suspected); pruritus; urticaria; vertigo; vomiting.
- *Rare*: dyspnoea; hypoaesthesia; leucopenia; pancreatitis; pollakiuria; pyrexia; tinnitus; visual disturbance.
- *Not known*: anaphylaxis; arthralgia; congestive heart failure (discontinue); erectile dysfunction; hearing loss (transient); hepatitis (discontinue); hypokalaemia; hypertriglyceridaemia; myalgia; neutropenia; peripheral neuropathy (discontinue); pulmonary oedema; severe skin reactions (e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis); thrombocytopenia; urinary incontinence.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Absorption of itraconazole capsules is pH-dependent (*not oral solution*). Drugs that raise gastric pH can reduce oral bioavailability and result in sub-therapeutic plasma concentrations (e.g. *antacids*, *lansoprazole*, *omeprazole*, *ranitidine*). *Antacids* should be administered *at least 2 hours after* the intake of itraconazole capsules. Patients receiving H_2-antagonists or PPIs should take itraconazole capsules with an acidic drink such as orange juice or cola.
- Itraconazole is a substrate of CYP3A4; it is also a strong inhibitor of CYP3A4 and P-gp. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Alfentanil*—increased risk of alfentanil toxicity; dose reduction may be necessary.
- *Carbamazepine*—risk of carbamazepine toxicity (avoid combination or monitor closely); risk of itraconazole therapeutic failure.
- *Ciclosporin*—risk of ciclosporin toxicity.
- *Clarithromycin*—risk of itraconazole toxicity; potential risk of prolongation of the QT interval (increased clarithromycin exposure).
- *Dexamethasone*—increased effect; dose reduction may be necessary.
- *Digoxin*—dose reduction may be necessary (P-gp inhibition).

- *Domperidone*—risk of prolonged QT interval due to increased domperidone plasma concentrations.
- *Erythromycin*—risk of itraconazole toxicity.
- *Fentanyl*—increased risk of fentanyl toxicity; dose reduction may be necessary.
- *Methadone*—increased risk of methadone toxicity; dose reduction may be necessary; risk of prolonged QT interval.
- *Midazolam*—increased risk of midazolam toxicity—use lower initial doses; dose adjustments may be necessary if itraconazole is added or discontinued (*NB—oral midazolam is contraindicated due to risk of toxicity*).
- *Mirtazapine*—risk of increased exposure to mirtazapine.
- *Naloxegol*—risk of excessive exposure to naloxegol (the SmPC advises to avoid combination).
- *Phenytoin*—risk of itraconazole therapeutic failure.
- *Quetiapine*—concurrent use of CYP3A4 inhibitors is contraindicated.
- *Reboxetine*—risk of reboxetine toxicity.
- *Theophylline*—risk of theophylline toxicity; dose reduction may be necessary.
- *Warfarin*—risk of raised INR.
- *Zopiclone*—increased plasma concentration and effects of zopiclone.

Pharmacodynamic

- *Calcium channel blockers*—increased risk of congestive heart failure due to negative inotropic effects.

Dose

Standard doses for oral candidosis are described here. Refer to local guidelines for other infections and advice.

Oral/oesophageal candidosis that has not responded to fluconazole

- Oral solution: 10mL to 20mL (100mg to 200mg) PO BD for 14 days. Use the solution as a mouthwash and swallow. Ensure the patient does not rinse the mouth afterwards.

Oral/oesophageal candidosis in HIV-positive or other immunocompromised patients

- Oral solution: 10mL to 20mL (100mg to 200mg) PO BD for 7 days. If there is no response after 1 week, treatment should be continued for another week. Use the solution as a mouthwash and swallow. Ensure the patient does not rinse the mouth afterwards.

Dose adjustments

Elderly

- The manufacturers state that itraconazole should not be used in the elderly unless the potential benefit outweighs the potential risks.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. The SmPC recommends caution and dose adjustments may be considered since itraconazole is predominantly metabolized by the liver.

- No specific guidance is available for patients with renal impairment. The oral bioavailability may be reduced in patients with renal impairment and a dose adjustment may be considered. Refer to the SmPC for IV use.
- In both cases, monitoring of plasma levels may be necessary.

Additional information

- The oral solution should be taken without food and patients must be advised to avoid eating for at least 1 hour after intake.
- The capsules must be taken with food for maximal absorption.
- Be aware of the potential for drug interactions with itraconazole.

Pharmacology

Itraconazole is rapidly absorbed after oral administration and is extensively metabolized by the liver via CYP3A4 into several metabolites. Plasma concentrations of hydroxy-itraconazole, an active metabolite with similar anti-fungal activity to itraconazole, are about double those of itraconazole. Metabolism is saturable. Less than 0.05% of a dose is excreted unchanged by the kidneys. The majority of a dose is excreted as inactive metabolites in the urine and faeces.

Ketamine ⚠

Due to the spatial arrangement of its molecular structure, ketamine exists as a racemic mixture comprising two enantiomers: S(+) ketamine (or esketamine) and R(−) ketamine (or arketamine). Vesierra® (esketamine) is available in the UK, but uses and doses discussed in this monograph refer to racemic ketamine only.

Ketalar® (CD2 POM)
Injection: 10mg/mL (20mL vial); 50mg/mL (10mL vial).
See ➔ *Additional information*, p. 376 for supply issues.

Generic (CD2 POM)
Injection: 50mg/mL (10mL vial).

Unlicensed special (CD2 POM)
Oral solution: 50mg/5mL (available in a variety of volumes and flavours).
See ➔ *Additional information*, p. 376 for supply issues.

Indications

- ⁺Refractory cancer pain.[1]
- ⁺Treatment resistant depression.[1]

Contraindications and cautions

- Ketamine is contraindicated for use in patients:
  - with raised intracranial pressure
  - where a rise in BP may pose a serious hazard
  - with severe coronary or myocardial disease, CVA, or cerebral trauma.
- Avoid in acute porphyria.
- For end-of-life care, the prescriber must carefully consider these conditions as some should not necessarily be a deterrent to use, providing the dose is carefully titrated.
- Use with caution in patients with cardiac failure, epilepsy, hepatic impairment (severe—see ➔ *Dose adjustments*, p. 376), hypertension, ischaemic heart disease, or previous CVA.
- If the patient has been receiving ketamine for ≥3 weeks, avoid sudden cessation of treatment. There are reports of hyperalgesia and allodynia following sudden withdrawal of SUBCUT ketamine infusion.
- Continuous use of ketamine has been reported to cause urinary tract symptoms such as urinary frequency, incontinence, and haemorrhagic cystitis. This is believed to occur with prolonged use (e.g. >5 months), although there are case reports of earlier development. If symptoms develop in the absence of urinary tract infection, a urologist should be consulted. If ketamine is considered to be the cause, it should be withdrawn gradually. In most cases, symptoms improve after discontinuation, although there are reports of irreversible renal impairment.
- Dose adjustments may be necessary in the elderly and liver impairment (see ➔ *Dose adjustments*, p. 376).

- Ketamine may cause drowsiness and dizziness. Patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Avoid grapefruit juice with oral ketamine.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects for licensed indications. Given the manner in which ketamine is used in palliative care, the type and incidence of adverse effects are difficult to judge. Nonetheless, many adverse effects are dose-related. At low doses employed for pain management, anticipated adverse effects would be mild and transient impairments in attention and memory. Anxious patients may be more at risk. Adverse effects from oral use tend to be less intense. The following have been reported from observational studies in different populations:

- abnormal LFTs; confusion; cystitis (may be haemorrhagic); delirium; dizziness; dysphasia; excessive salivation; euphoria; hallucinations; hypertension (possibly caused by potentiation of 5-HT_{2A} effects); nightmares; pain and inflammation around injection site; sedation; tachycardia; vivid dreams; visual disturbances.

Drug interactions

Pharmacokinetic

- Ketamine is metabolized by CYP2B6, CYP2C9, and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Clarithromycin*—increases plasma concentration of esketamine after PO administration; a similar effect is anticipated for PO racemic ketamine.
- *Grapefruit juice*—increases plasma concentration of esketamine after PO administration; a similar effect is anticipated for PO racemic ketamine.

Pharmacodynamic

- *CNS depressants*—risk of excessive sedation.
- *Opioids*—dose of opioid should be reviewed when ketamine is introduced; there is likely to be an opioid-sparing effect, necessitating a dose reduction.

Dose

+*Refractory cancer pain*

- Some patients may experience dysphoria or hallucinations with ketamine. Anxious patients are believed to be more at risk. Consider introducing the following before starting ketamine: diazepam 5mg PO ON, or midazolam 5mg to 10mg via CSCI, or haloperidol 2.5mg PO ON or 2.5mg SUBCUT ON or via CSCI.
- Until definitive evidence is available, when converting from SUBCUT to PO after several days of treatment, a conversion of 1:1 is suggested; when converting from SUBCUT to PO after *prolonged use* (e.g. weeks),

a conversion of 3:1 is suggested. Until definitive evidence is available, when converting routes, it is advisable to use a small dose initially and titrate accordingly. There should be provision for close monitoring and ability to alter the dose as necessary.[2,3] When switching from PO to CSCI, it is advisable to follow the initial dose schedule as shown below.

+Burst ketamine

- *Note that a randomized controlled trial concluded that 'burst' ketamine was no better than placebo.*[4] *Although not yet established, it is possible that patients experiencing both depression and pain may see the greatest reduction in symptoms.*
- It is advisable to reduce any concurrent total opioid dose by 30–50% prior to commencing ketamine.
- At all the doses below, the effective dose is continued for 3 days only.
- Initial dose 100mg over 24 hours via CSCI. Review after 24 hours. If effective, continue for a further 2 days.
- If ineffective, increase dose to 300mg over 24 hours via CSCI. Review after 24 hours. If effective, continue for a further 2 days (i.e. 3 days at 300mg).
- If ineffective, increase dose to 500mg over 24 hours via CSCI. Review after 24 hours. If ineffective, discontinue treatment and review. If effective, continue for a further 2 days (i.e. 3 days at 500mg).
- Burst ketamine has been shown to relieve pain in up to 50% of patients with intractable pain for at least 2 weeks; some patients may remain pain-free for several months. Treatment has been repeated at 4- to 8-weekly intervals.

+By CSCI

- Initial dose 50mg to 150mg over 24 hours (approximately 1 to 2.5mg/kg).
- Dose can be increased by 50mg to 100mg every 24 hours until benefit is achieved. If no response or significant benefit with 500mg, ensure the patient is reviewed before increasing the dose further. Doses above 600mg over 24 hours should be under specialist guidance only.
- Treatment should be reviewed once adequate analgesia has been achieved, with the intent to gradually reduce the dose and discontinue treatment over an arbitrary period (e.g. 1–3 weeks).
- If pain recurs, consider a further course of treatment.

+Oral

- Initial dose 10mg to 25mg PO TDS to QDS. Increase in steps of 10mg to 25mg TDS to QDS, to a maximum dose of 100mg PO QDS. Higher doses have been used under specialist guidance (e.g. up to 200mg PO QDS).
- Treatment should be reviewed once adequate analgesia has been achieved, with the intent to gradually reduce the dose and discontinue treatment over an arbitrary period (e.g. 1–3 weeks).
- If pain recurs, consider a further course of treatment.

+Treatment-resistant depression

(See ➔ *Additional information*, p. 376.)

- Evidence for benefit in depression is increasing but is limited to case reports or small studies.[5–7]
- The optimum dose, frequency, and route of administration are unclear.
- The majority of evidence utilizes a dose of up to 0.5mg/kg by IVI over 40 minutes.
- At least two small studies suggest SUBCUT injections are as efficacious as, and better tolerated than, IV administration:[6,7]
  - doses range from 0.1mg/kg to 0.5mg/kg SUBCUT.
- Evidence for PO administration is presently less convincing.
- The patient should be reviewed weekly and subsequent treatment will be individualized. Some patients may require doses twice a week, whereas others may require doses weekly or less frequently.

Dose adjustments

Elderly

- No information is available. Nonetheless, it is advisable to initiate treatment with lower doses than the ranges quoted above (e.g. 0.5 to 1mg/kg by CSCI or 5mg to 10mg PO TDS to QDS).

Hepatic/renal impairment

- Ketamine is hepatically metabolized. Although no information exists, it is advisable to initiate treatment with doses at the lower end of the quoted ranges.
- No dose adjustments should be necessary in renal impairment.

Additional information

Supply issues

Ketamine vials

- Ketamine injection is readily available in hospitals and the community. In the community, the patient should present the prescription to the pharmacist in the usual way. The community pharmacist can then place an order through a wholesaler.
- Supply should be made within 3 days of the request. The patient should be advised to request a prescription from the GP at least 5 days before the supply is needed.

Ketamine oral solution 50mg/5mL

- This unlicensed product is available as a special order from various suppliers.
- There are a variety of flavours (e.g. aniseed, peppermint) and volumes available. The flavour should be specified on the prescription; if not, determine the patient's preference.
- It can take up to 7 days for delivery. The patient should be advised to request a prescription from the GP at least 10 days before the supply is needed.

Extemporaneous preparation of ketamine oral solution

- The injection can be used directly from the vial, although flavouring will be needed to mask the taste (e.g. fruit juice, but *not* grapefruit).
- Alternatively, the injection can be transferred from the vial and diluted with a suitable vehicle (e.g. Raspberry Syrup BP or purified water) to

a concentration of 50mg/5mL. If purified water is used, the patient should be advised to use a flavouring to mask the taste.
- The extemporaneous product has an expiry of 7 days and should be refrigerated.

CSCI issues
- The injection may be irritant, and infusions should be maximally diluted with NaCl. Low-dose dexamethasone (0.5mg to 1mg) can be added to the infusion to help prevent site reactions.
- Ketamine is reportedly *chemically and physically* compatible under stated conditions in combination with dexamethasone, hydromorphone, midazolam, morphine sulfate, morphine tartrate, and oxycodone.[8]
- Ketamine via CSCI is reportedly *physically* compatible in combination under stated conditions with haloperidol, levomepromazine, and ranitidine.[5]

Depression
- Ketamine has been shown to be an extremely effective treatment for major depression, bipolar disorder, and suicidal behaviour. Its clinical effect appears incredibly fast, improving depression in as little as 2 hours, unlike conventional antidepressants which may take weeks. In the United States, esketamine in the form of a nasal spray has recently been approved by the FDA for the management of treatment-resistant depression, although this was rejected by NICE in early 2020.

Pharmacology

Ketamine has a unique pharmacology, facets of which are still being elucidated, that explains its array of clinical effects. It interacts with a specific binding site on the *N*-methyl-*D*-aspartate (NMDA) receptor complex, blocking the influx of Na^+ and Ca^{2+}. Other pharmacological mechanisms include interaction with MORs and DORs and the nicotinic receptor, muscarinic receptor, σ_1 and σ_2 receptors, D_2 receptor, 5-HT_{1B} receptor, and innate repair receptor (activates anti-inflammatory and tissue repair pathways), and potentiation of the 5-HT_{2A} receptor. Ketamine may modulate descending pain pathways, as well as producing anti-inflammatory effects.

Ketamine exists as a racemic mixture comprising two enantiomers: S(+) ketamine (or esketamine) and R(−) ketamine (or arketamine). Esketamine is 3–4 times more potent than arketamine and about twice as potent as the racemic mixture for the NMDA receptor. It is poorly absorbed after oral administration and undergoes extensive first-pass metabolism, resulting in a bioavailability of 17–24%. The major metabolic pathway is N-demethylation by CYP3A4 and CYP2B6 to a less active metabolite norketamine; CYP2C9 is thought to have a minor role. CYP2B6 polymorphisms have been associated with variation in ketamine steady-state concentrations. Ketamine is believed to enhance its own metabolism through enzyme induction, although the clinical implications of this are currently unknown. Norketamine has been shown to have anti-nociceptive properties in animal studies, but its analgesic effects in humans remain unclear.

The analgesic effect of ketamine that is seen at sub-anaesthetic doses is due to non-competitive antagonism of the NMDA receptor. Binding of

ketamine will only occur when the ion channel has been opened through neuronal excitation. The analgesic activity is believed to be due to attenuation of the 'wind-up' phenomenon by reducing the excitability of the neurone. The antidepressant effect of ketamine is thought to be caused by NMDA receptor antagonism, which produces a transient increase in glutamate release, leading to increases in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) stimulation. This subsequently leads to increases in neurotrophic signalling that restores synaptic function in the prefrontal cortex and hippocampus, and reversal of depression. Ketamine has recently been shown to bind to the 5-HT_{1B} receptor, which may also contribute to this effect.

References

1. Goldman N, Frankenthaler L, Klepacz L. The efficacy of ketamine in the palliative care setting: a comprehensive review of the literature. *J Palliat Med*. 2019;**22**(9):1154–61.
2. Benitez-Rosario MA, Salinas-Martin A, Gonzalez-Guillermo T, Feria M. A strategy for conversion from subcutaneous to oral ketamine in cancer pain patients: effect of a 1:1 ratio. *J Pain Symptom Manage*. 2011;**41**(6):1098–105.
3. Fitzgibbon EJ, Hall P, Schroder C, Seely J, Viola R. Low dose ketamine as an analgesic adjuvant in difficult pain syndromes: a strategy for conversion from parenteral to oral ketamine. *J Pain Symptom Manage*. 2002;**23**(2):165–70.
4. Hardy J, Quinn S, Fazekas B, *et al*. Randomized, double-blind, placebo-controlled study to assess the efficacy and toxicity of subcutaneous ketamine in the management of cancer pain. *J Clin Oncol*. 2012;**30**(29):11–17.
5. Sexton J, Atayee RS, Bruner HC. Case report: ketamine for pain and depression in advanced cancer. *J Palliat Med*. 2018;**21**(11):1670–3.
6. George D, Gálvez V, Martin D, *et al*. Pilot randomized controlled trial of titrated subcutaneous ketamine in older patients with treatment-resistant depression. *Am J Geriatr Psychiatry*. 2017;**25**(11):1199–209.
7. Loo CK, Gálvez V, O'Keefe E, *et al*. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand*. 2016;**134**(1):48–56.
8. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Ketorolac ⚠

Toradol® (POM)
Injection: 30mg/mL (5).

Generic (POM)
Injection: 30mg/mL (5).

Indications

- Short-term management of moderate to severe acute post-operative pain (*not discussed*).
- ǂManagement of refractory cancer pain.[1,2]

Contraindications and cautions

- Contraindicated for use in patients with:
  - cerebrovascular bleeding (confirmed or suspected)
  - complete or partial syndrome of nasal polyps, angioedema, or bronchospasm
  - concurrent treatment with aspirin, other NSAIDs including COX-2 inhibitors, anticoagulants including low-dose heparin or warfarin, pentoxifylline, probenecid, or lithium (see ➔ *Drug interactions*, p. 380)
  - haemorrhagic diatheses, including coagulation disorders
  - hepatic failure
  - history of, or active, peptic ulceration
  - hypersensitivity reactions to ibuprofen, aspirin, or other NSAIDs (e.g. asthma, rhinitis, angioedema, or urticaria)
  - hypovolaemia from any cause or dehydration (at risk of renal failure)
  - moderate or severe renal impairment (SeCr >160micromol/L)
  - severe heart failure.
- Ketorolac may be associated with a high risk of renal impairment and serious GI toxicity, relative to some other NSAIDs, especially when used outside the licensed indications and/or for prolonged periods. For end-of-life care, the prescriber must carefully consider these conditions as some should not necessarily be a deterrent to use, providing the dose is carefully titrated.
- Use the minimum effective dose for the shortest duration necessary to reduce the risk of cardiac and GI events. In the absence of benefit, other options should be considered.
- Elderly patients are more at risk of developing adverse effects.
- Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease need careful consideration due to the increased risk of thrombotic events.
- Similar consideration should be made before initiating longer-term treatment for patients with risk factors for CV events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).
- Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension. Deterioration may occur due to fluid retention.

- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk within the first month of treatment. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with ketorolac must not be restarted.
- Ketorolac may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Ensure co-prescription of misoprostol or a PPI (if appropriate) to address GI toxicity.
- Refer to ➔ Chapter 2, *Selection of an NSAID*, p. 49 for further information about selecting an NSAID.
- Ketorolac may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a detailed list of adverse effects. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms. The frequency of adverse effects in the UK SmPC is not defined; however, the US SmPC states the following:

- *Very common*: headache; nausea.
- *Common*: abnormal renal failure; abdominal pain; anaemia; coagulopathy; constipation; diarrhoea; dizziness; drowsiness; elevated LFTs; GI haemorrhage; GI ulcer; hypertension; oedema; pain at injection site (less so for CSCI); pruritus; stomatitis; sweating; tinnitus; vomiting.
- *Rare*: abnormal dreams; abnormal thinking; congestive heart failure; depression; dry mouth; dyspnoea; euphoria; fever; hallucinations; infections; insomnia; leucopenia; pallor; palpitation; paraesthesia; rhinitis; sepsis; syncope; tachycardia; taste abnormality; thrombocytopenia; visual disturbances.
- *Not known*: aseptic meningitis; flank pain with or without haematuria; hyperkalaemia; hypersensitivity reactions (e.g. anaphylaxis, bronchospasm); hyponatraemia; Stevens–Johnson syndrome; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Ketorolac is metabolized in the liver, mainly by glucuronidation, and is presently not known to be involved in metabolic drug interactions.
- *Lithium*—increased risk of lithium toxicity due to reduced renal clearance.
- *Methotrexate*—reduced excretion of methotrexate.

Pharmacodynamic

- *ACE-Is/ARBs*—risk of AKI.
- *Anticoagulants*—increased risk of bleeding (*concurrent use contraindicated*).

- *Antihypertensives*—reduced hypotensive effect.
- *Antiplatelet drugs*—increased risk of bleeding (*concurrent use contraindicated*).
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Corticosteroids*—increased risk of GI toxicity.
- *Diuretics*—reduced diuretic effect; risk of AKI.
- *Opioids*—dose of opioid should be reviewed when ketorolac is introduced; there is likely to be an opioid-sparing effect, necessitating a dose reduction.
- *Quinolone antibiotics*—risk of convulsions.
- *SSRIs*—increased risk of GI bleeding.

Dose

Gastroprotective treatment must be prescribed concurrently if appropriate. Consider misoprostol or a PPI if the oral route is available. Alternatively, ranitidine (if available) or esomeprazole via separate CSCI can be considered.

Dilute the CSCI to the largest possible volume with NaCl due to the irritant nature.

+Cancer pain

- Initial dose 10mg to 30mg SUBCUT TDS PRN.
- Alternatively, 60mg OD via CSCI, increasing to 90mg if necessary (but see ➔ *Dose adjustments*).

Dose adjustments

Elderly

- The elderly are at increased risk of adverse effects due to an increased plasma half-life and reduced plasma clearance of ketorolac. Initial dose 30mg OD via CSCI, increasing by 15mg/day increments to a maximum recommended dose of 60mg/day.

Hepatic/renal impairment

- In hepatic impairment, no specific dose recommendations are available. However, the lowest dose possible should be used for the shortest duration possible. Elevated LFTs may occur that may progress, may remain unchanged, or may be transient with continuing therapy. Ketorolac should be discontinued in patients who display clinical signs and symptoms consistent with liver disease.
- Ketorolac must not be used in patients with moderate to severe renal impairment. In patients with mild renal impairment, the dose used should not exceed 60mg/day.

Additional information

- Ensure concurrent opioid requirements are reviewed. As well as being an analgesic through COX-1 and COX-2 inhibition, ketorolac has been shown to reverse opioid tolerance and hyperalgesia, which may explain its apparent opioid-sparing effects.[3]
- The risk of clinically serious GI bleeding is dose-dependent. This is particularly true in elderly patients who receive an average daily dose of >60mg/day of ketorolac.

- Ketorolac via CSCI should be diluted with NaCl and administered as a separate infusion unless compatibility data are available. There is a risk of incompatibility with many drugs given via CSCI since ketorolac has an alkaline pH. However, it is reportedly *chemically* and *physically* compatible under stated conditions with diamorphine and tramadol. It is reportedly *physically* compatible under stated conditions with fentanyl, methadone, morphine sulfate, and oxycodone.[4]
- Ketorolac may precipitate in solutions with a low pH and is reportedly incompatible with cyclizine, haloperidol, morphine, and promethazine. There are mixed reports of incompatibility with hydromorphone. Glycopyrronium is likely to be incompatible due to the alkaline pH of ketorolac.[4]

Pharmacology

Ketorolac exhibits anti-inflammatory, analgesic, and antipyretic activity, although the analgesic effect appears to be the predominant action. The mechanism of action of ketorolac, like that of other NSAIDs, is not completely understood but may be related to inhibition of COX-1 and COX-2. The major metabolic pathway is glucuronic acid conjugation and about 90% of a dose is excreted in the urine as unchanged drug metabolites.

References

1. Vacha ME, Huang W, Mando-Vandrick J. The role of subcutaneous ketorolac for pain management. *Hosp Pharm*. 2015;**50**(2):108–12.
2. Vadivelu N, Gowda AM, Urman RD, *et al*. Ketorolac tromethamine—routes and clinical implications. *Pain Pract*. 2015;**15**(2):175–93.
3. Davis MP. Opioid tolerance and hyperalgesia: basic mechanisms and management in review. *Prog Palliat Care*. 2011;**19**(2):73–86.
4. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Lactulose

Generic (P)
Solution: 3.1–3.7g/5mL (300mL; 500mL).
Sachets: 10g/15mL oral solution per sachet.

Indications

- Treatment of constipation.
- Treatment of hepatic encephalopathy.

Contraindications and cautions

- Contraindicated for use in:
  - galactosaemia
  - intestinal obstruction.
- Use with caution in patients with lactose intolerance.

Adverse effects

Refer to the manufacturer's SmPC for a detailed list of adverse effects.

- *Very common*: abdominal pain; flatulence (should improve after a few days' treatment).
- *Common*: diarrhoea; nausea; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None known.

Pharmacodynamic

- *5-HT$_3$ antagonists*—antagonizes the laxative effect.
- *Anticholinergics*—antagonizes the laxative effect.
- *Cyclizine*—antagonizes the laxative effect.
- *Opioids*—antagonizes the laxative effect.
- *TCAs*—antagonizes the laxative effect.

Dose

Constipation

- Initial dose 15mL PO BD, adjusted to the patient's needs.

Hepatic encephalopathy:

- Initial dose 30–50mL PO TDS, adjusted to produce 2–3 soft stools each day.

Dose adjustments

Elderly

- No dose adjustment necessary.

Hepatic/renal impairment

- No dose adjustment necessary.

Additional information

- Can take up to 48 hours for the laxative effect to work.

Pharmacology

Lactulose is a synthetic sugar consisting of fructose and galactose. In the colon, it is broken down primarily to lactic acid by the action of colonic bacteria. This results in an increase in osmotic pressure and a slight reduction of colonic pH, which cause an increase in stool water content and softens the stool. In the treatment of hepatic encephalopathy, it is thought that the low pH reduces the absorption of ammonium ions and other toxic nitrogenous compounds.

Lansoprazole ♡

Zoton Fastabs® (POM)
Orodispersible tablet: 15mg (28); 30mg (28).

Generic (POM)
Capsule (enclosing e/c granules): 15mg (28); 30mg (28).
Orodispersible tablet: 15mg (28); 30mg (28).

Indications

- Treatment of gastric and duodenal ulcer.
- Treatment and prophylaxis of reflux oesophagitis.
- Treatment and prophylaxis of NSAID-associated benign gastric and duodenal ulcers requiring continual therapy.
- Symptomatic gastro-oesophageal reflux disease.
- Eradication of *Helicobacter pylori* (*not discussed*).
- Zollinger–Ellison syndrome (*not discussed*).

Contraindications and cautions

- Increased gastric pH resulting from lansoprazole treatment may critically affect the absorption of certain drugs (see ➔ *Drug interactions*, p. 386).
- Treatment with lansoprazole may lead to a slightly increased risk of developing GI infections (e.g. *Clostridium difficile*). Therefore, avoid unnecessary use or high doses.
- Orodispersible tablets contain aspartame—avoid in phenylketonuria.
- Rebound acid hypersecretion may occur on discontinuation if the patient has received >8 weeks' treatment.
- Lansoprazole is predominantly metabolized by CYP2C19 and CYP3A4 to a lesser extent. Factors affecting CYP2C19 activity, such as phenotype (see Box 1.3) and drugs (see ➔ *Drug interactions*, p. 386), can alter response and adverse effects.
- PPIs are associated with a range of electrolyte disturbances such as hyponatraemia and hypomagnesaemia (and associated hypocalcaemia and hypokalaemia). Suspect the PPI, should unexplainable symptoms present (e.g. confusion, delirium, generalized weakness, nausea). The effect on Na^+ metabolism is unclear, possibly involving ADH. PPIs may reduce active Mg^{2+} absorption in the small intestine by affecting the function of a transient receptor protein channel. Poor metabolizer status may contribute to such adverse effects.
- There is a *conditional* risk of QT prolongation/TdP due to the propensity to cause significant electrolyte disturbances (e.g. hypokalaemia or hypomagnesaemia). Monitor electrolytes regularly in patients with known QT interval prolongation or congenital long QT syndrome and in those taking drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 386).
- When used in high doses and over long durations (>1 year), PPIs may increase the risk of hip, wrist, and spine fracture predominantly in the elderly or in the presence of other recognized risk factors. Consider the need for adequate vitamin D and calcium intake.

- Lansoprazole may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the manufacturer's SmPC for a detailed list of adverse effects.

- *Common*: headache; nausea.
- *Uncommon*: abnormal renal failure; abdominal pain; anaemia; coagulopathy; constipation; diarrhoea; dizziness; drowsiness; elevated LFTs; GI haemorrhage; GI ulcer; hypertension; oedema; pain at injection site (less so for CSCl); pruritus; stomatitis; sweating; tinnitus; vomiting.
- *Rare*: abnormal dreams; abnormal thinking; congestive heart failure; depression; dry mouth; dyspnoea; euphoria; fever; hallucinations; infections; insomnia; leucopenia; pallor; palpitation; paraesthesia; rhinitis; sepsis; syncope; tachycardia; taste abnormality; thrombocytopenia; visual disturbances.
- *Very rare*: aseptic meningitis; flank pain with or without haematuria; hyperkalaemia; hypersensitivity reactions (e.g. anaphylaxis, bronchospasm); hyponatraemia; Stevens–Johnson syndrome; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Lansoprazole is metabolized mainly by CYP2C19, with a minor role involving CYP3A4. It can weakly induce CYP1A2. It may have inhibitory effects on CYP3A4 (as stated by the SmPC), but the clinical significance is currently unclear. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- P-gp is inhibited by lansoprazole, but the clinical significance is presently unknown.
- Lansoprazole does not have a clinically significant inhibitory effect on CYP2C19 (unlike esomeprazole and omeprazole).
- Drugs with pH-dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced
  - *iron supplements*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g. 200mg per 30mg elemental iron) at the same time as the iron supplement to improve absorption

  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations
  - *metronidazole suspension*—lansoprazole may reduce/prevent the absorption of metronidazole.
- *Antacids*—should be given at least 1 hour before lansoprazole (reduced bioavailability).
- *Azole antifungals*—fluconazole may cause increased lansoprazole concentrations (CYP2C19 inhibition).
- *Methotrexate*—lansoprazole may cause increases in levels of methotrexate; consider withholding lansoprazole.
- *Theophylline*—lansoprazole can reduce the plasma concentration of theophylline (CYP1A2 induction).

Pharmacodynamic

- Lansoprazole may cause prolongation of the QT interval due to the propensity to cause electrolyte disturbances. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Corticosteroids*—concurrent use may increase the risk of osteoporosis and osteoporotic fractures.

Dose

Treatment of peptic ulcer disease

- 30mg PO OD for 2–4 weeks.
- Gastric ulcer treatment may need to continue for 4–8 weeks.

Reflux oesophagitis

- Treatment: 30mg PO OD for 4–8 weeks.
- Prophylaxis: 15mg to 30mg PO OD as necessary.

NSAID-associated benign gastric and duodenal ulcers

- Treatment: 30mg PO OD for 4 weeks, continuing to 8 weeks if not fully healed; 30mg PO BD can be considered.
- Prophylaxis: 15mg to 30mg PO OD.

Symptomatic gastro-oesophageal reflux disease

- 15mg to 30mg PO OD. Review after 4 weeks if symptoms persist.

NB—there is little evidence to recommend routine prescribing of lansoprazole 30mg PO OD for dyspeptic symptoms. If 30mg PO OD fails to control such symptoms, treatment should be combined with antacids (given at least 1 hour before lansoprazole) such as Gaviscon®.

Dose adjustments

Elderly

- 30mg PO OD should not usually be exceeded unless there are compelling clinical reasons.

Hepatic/renal impairment

- A 50% dose reduction is recommended in moderate to severe hepatic impairment.
- No dose adjustment is necessary in renal impairment.

Additional information

- Lansoprazole capsules containing enteric-coated granules may be opened and emptied into a glass of orange juice or apple juice, mixed and swallowed immediately. The glass should be rinsed with additional juice to ensure complete delivery of the dose. The intact enteric-coated granules should not be chewed or crushed.
- The orodispersible tablet can be dispersed in a small amount of water and administered via an 8-Fr nasogastric tube.
- Symptoms can be relieved following the first dose.

Pharmacology

Lansoprazole is a gastric PPI, reducing the release of H^+ from parietal cells by inhibiting H^+/K^+ ATPase. It is rapidly inactivated by gastric acid; hence oral formulations are enteric-coated. Oral bioavailability is high (≈ 90%), but administration with food can reduce this. It is extensively metabolized, mainly by CYP2C19, although an alternative pathway involves CYP3A4. Note that CYP2C19 poor metabolizers (or patients taking CYP2C19 inhibitors) can have significantly higher plasma concentrations, leading to unexpected results. Metabolites are virtually inactive and are eliminated by both renal and biliary excretion.

Letrozole

Femara® (POM)
Tablet: 2.5mg (30).

Generic (POM)
Tablet: 2.5mg (14; 28).

Indications

- Treatment (primary or adjuvant) of post-menopausal women with hormone receptor-positive invasive early breast cancer.

Contraindications and cautions

- Letrozole is contraindicated for use in patients with premenopausal endocrine status.
- It should be used with caution in patients with:
  - history of osteoporosis or bone fractures
  - severe hepatic impairment
  - severe renal impairment (CrCl <10mL/min).
- May cause reduction in bone mineral density. Patients at risk may need bone mineral density assessment prior to treatment. Treatment for osteoporosis may be required.
- Fatigue and dizziness have been reported with letrozole. Caution should be observed when driving or operating machinery while such symptoms persist. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: arthralgia; asthenia; fatigue; hot flushes; hypercholesterolaemia; hyperhidrosis.
- *Common*: alopecia; appetite changes (increase and decrease reported); arthritis; bone fractures; bone pain; chest pain; constipation; depression; diarrhoea; dizziness; dry skin; dyspepsia; haemorrhage (vaginal); headache; hypertension; myalgia; osteoporosis; nausea; palpitations; peripheral oedema; rash (erythematous, maculopapular, vesicular); vomiting; weight gain.
- *Uncommon*: anxiety; carpal tunnel syndrome; CVA; cough; drowsiness; dry mouth; dysgeusia; dyspnoea; hypoaesthesia; insomnia; irritability; ischaemic cardiac events (angina, myocardial infarction); leucopenia; raised LFTs (hyperbilirubinaemia, jaundice); memory impairment; paraesthesia; pollakiuria; pruritus; pyrexia; stomatitis; tachycardia; thrombophlebitis; tumour pain; urinary tract infection; urticaria; vaginal discharge; visual disturbances (blurred vision, cataract, eye irritation); vulvovaginal dryness; weight loss.
- *Rare*: arterial thrombosis; cerebral infarction; PE.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Letrozole is metabolized by CYP2A6 and CYP3A4; it inhibits CYP2A6 and also moderately affects CYP2C19. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Letrozole is unlikely to be a cause of many drug interactions since CYP2A6 does not have a major role in drug metabolism. At usual doses, letrozole is unlikely to affect CYP2C19 substrates.

Pharmacodynamic

- None known.

Dose

- 2.5mg PO OD.

Dose adjustments

Elderly

- No dose adjustments are necessary for elderly patients.

Hepatic/renal impairment

- No dose adjustments are necessary for patients with mild to moderate hepatic impairment. The manufacturer recommends close supervision of treatment in patients with severe hepatic impairment due to insufficient data.
- No dose adjustments are necessary for patients with CrCl ≥10mL/min. There are insufficient data below this value to make a dose recommendation. Nonetheless, approximately 6% of a dose is renally excreted as unchanged drug.

Additional information

- Letrozole should be continued for 5 years or until tumour relapse occurs.

Pharmacology

Letrozole is a non-steroidal aromatase inhibitor. It is believed to work by significantly lowering serum oestradiol concentrations through inhibition of aromatase (converts adrenal androstenedione to oestrone, which is precursor of oestradiol). Many breast cancers have oestrogen receptors and growth of these tumours can be stimulated by oestrogens.

Levetiracetam ⚠ ♀

Keppra® (POM)
Tablet: 250mg (60); 500mg (60); 750mg (60); 1000mg (60).
Oral solution (sugar-free): 100mg/mL (150mL; 300mL).
Concentrate for IVI: 500mg/5mL.

Generic (POM)
Tablet: 250mg (60); 500mg (60); 750mg (60); 1000mg (60).
Oral solution (sugar-free): 100mg/mL (150mL; 300mL).
Concentrate for IVI: 500mg/5mL.

Indications

- Treatment of partial-onset seizures with or without secondary generalization (in patients from 16 years old).
- Adjunctive therapy of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalized tonic–clonic seizures.
- ⁺Management of status epilepticus.[1]
- ⁺Management of seizures by CSCI.[2]

Contraindications and cautions

- As with all anti-epileptics, avoid abrupt withdrawal. The manufacturer advises in adults and adolescents weighing >50kg, no more than 500mg decreases BD every 2–4 weeks.
- Use with caution in patients with hepatic or renal impairment (see ➔ *Dose adjustments*, p. 393).
- Despite the *CredibleMeds® possible* risk of dose-related QT prolongation/TdP with levetiracetam, there are no warnings of such in the UK SmPCs. Nonetheless, due consideration should be given to the risk when considering prescribing for patients with additional risk factors (e.g. electrolyte disorders, concurrent use of drugs known to affect the QT interval).
- Patients should be monitored for signs of suicidal ideation since anti-epileptic drugs have been associated with this behaviour.
- Levetiracetam may cause psychotic symptoms and behavioural abnormalities, including irritability and aggressiveness. If such symptoms develop, treatment adaptation or gradual discontinuation should be considered. Note that levetiracetam may precipitate symptoms such as agitated delirium when used for end-of-life management of seizures. If such symptoms develop, a suitable course of action may be withdrawal and substitution with midazolam or clonazepam.
- Levetiracetam may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: headache; nasopharyngitis; sedation.
- *Common*: abdominal pain; aggression; anorexia; asthenia; cough; depression; diarrhoea; dizziness; dyspepsia; fatigue; insomnia; irritability; nausea; nervousness; rash; tremor; vertigo; vomiting.

- *Uncommon*: agitation; alopecia (reversible on discontinuation); amnesia; ataxia; eczema; hallucination; leucopenia; abnormal LFTs; memory impairment; myalgia; paraesthesia; pruritus; panic attacks; psychotic disorder; suicidal ideation; thrombocytopenia; weight changes (gain or loss reported); visual disturbances (blurred vision, diplopia).
- *Rare*: AKI; agranulocytosis; dyskinesia; erythema multiforme; hepatitis; hypersensitivity reactions*; hyponatraemia; neutropenia; pancreatitis; pancytopenia; personality disorder; rhabdomyolysis; Stevens–Johnson syndrome; suicidal ideation; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Levetiracetam, unlike other anti-epileptics, has a low potential for pharmacokinetic drug interactions since drug-metabolizing systems are unaffected.
- Drugs excreted by renal tubular secretion (e.g. amiloride, cefalexin, digoxin, morphine, quinine) have the potential to interact with levetiracetam, increasing plasma concentrations. The clinical significance is presently unknown.
- Drugs which affect renal function have the potential to interact with levetiracetam. If such drugs are co-administered, regular monitoring of renal function is advisable. Such drugs include:
  - ACE-Is
  - NSAIDs.
- *Macrogol*—may reduce the effectiveness of levetiracetam; do not take macrogol within 1 hour of levetiracetam.

Pharmacodynamic

- *Antipsychotics*—seizure threshold lowered.
- *Antidepressants*—seizure threshold lowered.
- *CNS depressants*—risk of excessive sedation.
- *Tapentadol*—seizure threshold lowered.
- *Tramadol*—seizure threshold lowered.

Dose

Note that the SUBCUT/IV route can be substituted for the PO route at the same dose.

Monotherapy

- Initial dose 250mg PO OD, increased after 1–2 weeks to 250mg PO BD. Dose can be increased, as necessary, in steps of 250mg PO BD every 2 weeks to a maximum of 1500mg PO BD.

* A delayed hypersensitivity disorder (known as hypersensitivity syndrome or DRESS) may occur at any time during treatment (usually within 2–8 weeks of initiating treatment), with symptoms that may include fever, skin rash, lymphadenopathy, haematological abnormalities, hepatitis, and interstitial nephritis. Acute anaphylactic shock has been reported. If such reactions do occur, levetiracetam should be withdrawn immediately and permanently.

Adjunctive treatment

- Initial dose 500mg PO BD (or 250mg PO BD for patients <50kg). Dose can be increased, as necessary, in steps of 500mg PO BD every 2–4 weeks, to a maximum of 1500mg PO BD.

[+]Status epilepticus

- Check local policies.
- Suggested dose is 60mg/kg by IVI (maximum dose 4500mg) in 100mL of NaCl over 10 minutes.
- Subsequent treatment should be guided by local practice. For example:
  - if seizures have persisted for <30 minutes despite completion of the infusion, a second IV anticonvulsant should be considered (before anaesthesia)
  - if seizures respond to the initial infusion, a maintenance dose of 1000mg IV/PO BD is suggested (refer to ➔ *Dose adjustments* if eGFR is <60mL/min/1.73m^2)
  - the first dose of maintenance treatment should be given as close as possible to 12 hours after the initial loading dose described above; a range of 10–14 hours is acceptable in order to allow regular maintenance treatment during daytime hours.

[+]Administration by CSCI

- The initial dose of levetiracetam will depend upon the patient's previous requirements, although a 1:1 conversion from PO to SUBCUT (as CSCI) can be used.
- In situations where the patient has not previously received levetiracetam, there is limited information on how to proceed. One approach is to start at 1000mg by CSCI[+] over 24 hours and increase, as necessary, over 2–4 days to 3000mg by CSCI[+] over 24 hours.
- In order to avoid the need for two syringe pumps, it is possible to use a 50mL syringe on the BD BodyGuard T (formerly CME T34) syringe pump, permitting up to 37mL to be infused over 24 hours. [+]A lock box manufactured for CME T60 will fit around the BodyGuard T syringe pump with a 50mL syringe attached.

Dose adjustments

Elderly

- Dose adjustments may be necessary, based on renal function (see below).

Hepatic/renal impairment

- Dose adjustments are unnecessary in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, however, a dose reduction is recommended because CrCl may be unreliable; in patients with CrCl <80mL/min/1.73m^2, a reduction of the daily maintenance dose is recommended.
- Dose adjustments are necessary for patients with renal impairment or undergoing dialysis and must be individualized (refer to Table 3.14). Dose adjustments are based upon the patient's CrCl and body surface area (BSA):

$$CrCl_{adj} = \frac{CrCl}{BSA} \times 1.73$$

Table 3.14 Dose adjustments for patients >50kg with renal impairment

C rCl_{adj} (mL/min/1.73m^2)	Dose
>80	500mg to 1500mg BD PO/IV; 500mg to 3000mg CSCI
50–79	500mg to 1000mg BD PO/IV; 500mg to 2000mg CSCI
30–49	250mg to 750mg BD PO/IV; 250mg to 1500mg CSCI
<30	250mg to 500mg BD PO/IV; 250mg to 1000mg CSCI
End-stage renal disease patient undergoing haemodialysis*	500mg to 1000mg OD PO/IV**; 250mg–1000mg CSCI**

* A loading dose of 750mg levetiracetam is recommended on the first day of treatment.

** A supplementary dose of 250mg to 500mg is recommended following dialysis.

Additional information

- The oral solution may be diluted prior to administration if needed. Absorption is not affected by food or enteral feeds.
- For status epilepticus, the choice of second-line drug is based upon comorbidity, risk of drug interactions, current or previous anti-epileptic use, and underlying diagnosis.
- The concentrate for IVI must be diluted in at least 100mL of suitable diluent (e.g. NaCl or GLU) and administered over 15 minutes.
- Levetiracetam can be administered by CSCI at concentrations of up to 100mg/mL, although maximal dilution with WFI is recommended in order to preserve the infusion site. Dexamethasone 0.5mg may be added in an attempt to preserve the site if necessary. In addition, levetiracetam is anecdotally *physically* compatible in a CSCI with glycopyronnium, hyoscine butylbromide, midazolam, morphine sulfate, and oxycodone.

Pharmacology

The exact mechanism of action of levetiracetam is presently unknown. It is believed that the anti-epileptic activity relates to its binding to the synaptic vesicle protein SV2A, a protein important for normal neurotransmission. After oral administration, levetiracetam is rapidly and almost completely absorbed. It does not inhibit or induce drug metabolism to any significant degree and its main metabolic pathway does not involve CYP enzymes. Levetiracetam is excreted by the kidneys as either the unchanged drug (66%) or an inactive metabolite formed by hydrolysis (24%).

References

1. Chamberlain JM, Kapur J, Shinnar S, *et al*. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet*. 2020;**395**(10231):1217–24.
2. Sutherland AE, Curtin J, Bradley V, *et al*. Subcutaneous levetiracetam for the management of seizures at the end of life. *BMJ Support Palliat Care*. 2018;**8**(2):129–35.

Levomepromazine ♥

Nozinan® (POM)
Tablet (scored): 25mg (84).
Injection: 25mg/mL (10).

Generic (POM)
Injection: 25mg/mL (10).
Tablet: 6mg (28); 25mg (84); 50mg (84).

Unlicensed special (POM)
Oral solution: available in a variety of concentrations, volumes, and flavours (see ➔ *Additional information*, p. 398 below for supply issues).

Indications

- Terminal agitation.
- Nausea/vomiting (*tablet unlicensed*).
- Psychosis (*injection unlicensed*).

Contraindications and cautions

- There are no absolute contraindications to the use of levomepromazine in terminal care.
- For situations other than terminal care, the following precautions apply.

⚠ Warning

- Antipsychotic drugs have been associated with an elevated risk of VTE. Several potential mechanisms have been described, including drug-induced sedation, obesity, hyperprolactinaemia, increased platelet aggregation (by 5-HT_{2A} antagonism), and elevation of antiphospholipid antibody.
- A risk of excess mortality has been consistently observed in elderly patients with dementia treated with antipsychotics. The mechanism of mortality may be CV in nature (e.g. arrhythmia susceptibility from QT prolongation or increased risk of VTE). Conventional antipsychotics (e.g. haloperidol, levomepromazine) are likely to carry a greater risk of mortality than second-generation antipsychotics (e.g. quetiapine, risperidone).
- The risks associated with CVA (e.g. diabetes, hypertension, smoking) should be assessed before commencing treatment with levomepromazine.
- Avoid using in patients with dementia unless they are at immediate risk of harm or are severely distressed.

- Levomepromazine should be used with caution in patients with:
  - concurrent antihypertensive medication (see ➔ *Drug interactions*, p. 396)
  - diabetes mellitus (risk of hyperglycaemia in the elderly, increased risk of CVA)

  - epilepsy (may lower the seizure threshold)
  - hepatic impairment
  - Parkinson's disease (may worsen parkinsonian symptomatology, *but* low doses employed for nausea/vomiting may be tolerated)
  - postural hypotension.
- There is a *known* risk of QT prolongation/TdP with levomepromazine (the SmPC states very rarely):
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment.
- Concurrent use of adrenaline and antipsychotics may cause dose-dependent severe hypotension and tachycardia (the α-adrenergic antagonist effects of antipsychotics can result in decreased peripheral resistance, and adrenaline may have significant β2-adrenergic-mediated vasodilatory effects).
- Levomepromazine should be used with caution in ambulant patients over 50 years of age due to the risk of a hypotensive reaction.
- If a patient develops signs and symptoms indicative of NMS, such as altered mental status, autonomic instability (e.g. cardiac dysrhythmia, diaphoresis), hyperpyrexia, and muscle rigidity, or presents with unexplained high fever without additional clinical manifestations of NMS, levomepromazine must be discontinued.
- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Levomepromazine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: dry mouth; drowsiness.
- *Common*: asthenia; heat stroke; hypotension (especially in elderly patients); QT prolongation.
- *Uncommon*: agranulocytosis; constipation; convulsions; parkinsonism (prolonged high doses); VTE.
- *Rare*: jaundice; ventricular arrhythmias.
- *Unknown*: impaired glucose tolerance (hyperglycaemia); NMS; photosensitivity; SIADH; TdP; VTE.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Levomepromazine is an inhibitor of CYP2D6, with *in vitro* studies suggesting lesser inhibitory effects on CYP1A2 and CYP3A4. It is metabolized mainly by CYP3A4, with a minor pathway involving CYP1A2. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Codeine*: a dose of 25mg/day PO levomepromazine has been shown to significantly reduce O-demethylation of codeine to form morphine.[1]

Pharmacodynamic

- Levomepromazine can cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *erythromycin*, *haloperidol*, *quinine*) may result in ventricular arrhythmias.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Adrenaline*—α-adrenergic effects may be blocked, with consequential paradoxical hypotension and tachycardia.
- *Anticholinergics*—increased risk of adverse effects.
- *Antidiabetics*—impaired glycaemic control (risk of hyperglycaemia).
- *Anti-epileptics*—dose may need to be increased to take account of the lowered seizure threshold.
- *Antihypertensives*—increased risk of hypotension.
- *CNS depressants*—additive sedative effect.
- *Haloperidol*—may be an additive hypotensive effect; increased risk of extrapyramidal symptoms.
- *Levodopa and dopamine agonists*—effect antagonized by levomepromazine.
- *Metoclopramide*—increased risk of extrapyramidal symptoms.
- *Opioids*—may be an additive hypotensive effect.
- *Trazodone*—may be an additive hypotensive effect.

Dose

When prescribing levomepromazine, the SUBCUT dose *should* be lower than the corresponding PO dose (which undergoes significant first-pass metabolism). A separate prescription is recommended to ensure that doses for a given route are clearly defined. Nonetheless, many centres use the same PO/SUBCUT doses for the management of nausea/vomiting.

Levomepromazine when administered by IV injection must be diluted with an equal volume of normal saline immediately before use.

Psychosis

- Initial dose 25mg to 50mg PO daily in 2–3 divided doses. Larger doses can be given at bedtime. Doses can be increased, as necessary, to the most effective level compatible with sedation and other adverse effects.

- [+]Alternatively, by 10mg to 25mg IM/IV/SUBCUT[+] 2-hourly PRN, or via CSCI. Treatment can be continued via CSCI at doses of between 50 and 200mg daily. Higher doses, under specialist supervision, may be necessary.

Terminal agitation

- Initial dose 10mg to 25mg IM/IV/SUBCUT[+] 1- to 2-hourly initially (lower doses for frail or elderly, e.g. 2.5mg to 6.25mg). Treatment can be continued via CSCI at doses of between 50mg and 200mg daily. Higher doses, under specialist supervision, may be necessary.

Nausea and vomiting

- Initial dose [+]3mg to 6mg (or 6.25mg) PO ON. Additional doses can be given (e.g. 6mg 4- to 6-hourly PRN) to a maximum total dose of 24mg (or 25mg) daily.
- Regular daily doses are generally administered at bedtime, but the dose can be split if necessary (e.g. 6mg BD).
- [+]Alternatively, initial dose 2.5mg to 6.25mg SUBCUT ON, or via CSCI. Additional doses can be given (e.g. 2.5mg SUBCUT 4- to 6-hourly PRN) or to a maximum dose of 25mg daily.

Dose adjustments

Elderly

- No specific adjustments required. However, patients over the age of 50 years may be more susceptible to adverse effects such as postural hypotension and anticholinergic effects (with an increased risk of cognitive decline and dementia). Wherever possible, the lowest effective dose should be used.

Hepatic/renal impairment

- Wherever possible, lower doses should be used. Patients may be more susceptible to adverse effects.

Additional information

- Levomepromazine causes fewer extrapyramidal adverse effects, compared to chlorpromazine or haloperidol. This may be related to its high affinity for the 5-HT_3 receptor. Low doses used for nausea and vomiting (i.e. <25mg/day PO/SUBCUT) may be considered for use in patients with Parkinson's disease, with close observation.
- Tablets can be dispersed in water immediately prior to administration if necessary. Alternatively, tablets may be administered SUBLING; other options, however, may be preferable (e.g. orodispersible olanzapine).
- The injection may change colour if placed in direct sunlight (e.g. deep purple) and is incompatible with alkaline solutions (e.g. dexamethasone).
- In order to reduce the risk of site reactions, levomepromazine via CSCI should be diluted with NaCl.
- Levomepromazine is *chemically and physically* compatible under stated conditions with hydromorphone, morphine sulfate, and oxycodone. Under stated conditions, levomepromazine is *physically* compatible with diamorphine, fentanyl, and methadone. Levomepromazine is

incompatible with ranitidine and may show concentration-dependent incompatibility with dexamethasone and ketorolac.[2]
- Levomepromazine oral suspension is available as a special-order item from various suppliers.

Pharmacology

Levomepromazine is an antipsychotic drug that shares similar properties with chlorpromazine. It is an antagonist at the D_2 receptor, 5-$HT_{2A/2C}$ receptors, α_1-adrenergic receptor, H_1-receptor, and muscarinic receptor. Consequently, it has a wide spectrum of adverse effects. It is metabolized by various pathways to form numerous metabolites, several of which display similar activity to the parent molecule and may contribute to the action of the drug. N-demethylation and 5-sulfoxidation have been suggested to be the dominant pathways involved in levomepromazine metabolism; CYP3A4 is the cytochrome involved in the major route of metabolism for levomepromazine in humans, although CYP1A2 contributes to the formation of the sulfoxide metabolite. The significant involvement of CYP3A4 explains the first-pass effect and reduced oral bioavailability.

References

1. Vevelstad M, Pettersen S, Tallaksen C, Brors O. O-demethylation of codeine to morphine inhibited by low-dose levomepromazine. *Eur J Clin Pharmacol*. 2009;**65**(8):795–801.
2. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Lidocaine (infusion) ⚠

Generic (POM)

Injection solution: 5mg/mL (0.5%); 10mg/mL (1%); 20mg/mL (2%) (various pack sizes).

Indications

- +Refractory cancer pain.[1]
- +Intractable pruritus associated with T-cell lymphoma.[2]

Contraindications and cautions

- Refer to the manufacturer's SmPC for a detailed list of contraindications and cautions.
- Lidocaine is contraindicated for use in patients with:
  - allergy to amide anaesthetics
  - severe cardiac failure or complete heart block
  - uncontrolled seizures.
- Electrolyte disorders (i.e. hypokalaemia/hypomagnesaemia) *must* be corrected before considering treatment with parenteral lidocaine.
- Lidocaine must be used with caution in the following:
  - bradycardia
  - concurrent use with several other drugs (see ➔ *Drug interactions*, p. 401)
  - congestive cardiac failure
  - epilepsy
  - hepatic impairment (see ➔ *Dose adjustments*, p. 402)
  - hypertension (systolic BP >160mmHg)
  - myasthenia gravis
  - renal impairment (see ➔ *Dose adjustments*, p. 402)
  - respiratory depression
  - supraventricular arrhythmia.
- Elderly patients may be at risk of accumulation (see ➔ *Dose adjustments*, p. 402).
- The patient *must* be closely monitored before and during treatment with CSCI lidocaine (see ➔ *Monitoring*, p. 402).
- It may be appropriate to administer a test dose prior to commencement of a CSCI (see ➔ *Dose*, p. 402).
- The patient may need a dose reduction of any concomitant opioid analgesic.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. The use of lidocaine by CSCI is unlicensed and there is a paucity of experience. Nonetheless, adverse effects of lidocaine use can be divided into mild, moderate, or severe, depending on plasma concentrations. The adverse effect profile of lidocaine is very predictable, and it has a wide margin of safety. As plasma levels increase, the development of adverse effects is sequential and predictable, such that they can be easily managed by stopping or reducing the rate of infusion.[3]

- When used at the suggested doses for the management of pain (i.e. <2mg/kg/hr—see ➔ *Dose*, p. 402), plasma levels of lidocaine are usually within the range of 1 to 3 micrograms/mL.
- Mild adverse effects (at serum levels of <8 micrograms/mL) include:
  - feeling light-headed or dizzy
  - hypertension
  - metallic taste
  - numbness and tingling in fingers or toes or around the mouth
  - tinnitus.
- Moderate adverse effects (at serum levels of 8–12 micrograms/mL) include:
  - auditory disturbances (e.g. deafness)
  - drowsiness
  - hypotension
  - myoclonus
  - nausea
  - severe dizziness
  - visual disturbances (e.g. blurred vision).
- Severe adverse effects (at serum levels of >12 micrograms/mL) include:
  - cardiac arrest
  - cardiac arrhythmias
  - coma
  - respiratory arrest
  - seizures.
- A CSCI of lidocaine may cause a site reaction; site rotation may reduce the likelihood.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Lidocaine is metabolized by CYP1A2 and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Ciprofloxacin*—may reduce the elimination of lidocaine, increasing the risk of toxicity.
- *Erythromycin*—may reduce the elimination of lidocaine, increasing the risk of toxicity.
- *Fluvoxamine*—may reduce the elimination of lidocaine, increasing the risk of toxicity.

Pharmacodynamic

- There may be an increased risk of ventricular arrhythmia in patients treated concurrently with drugs that may prolong the QT interval.

Monitoring

- The following describes suggestions for ensuring the safe use of lidocaine infusions in palliative care. Nonetheless, local guidelines must be adhered to.
- Prior to commencing a CSCI of lidocaine, the following tests should be performed:
  - FBC; U&Es; LFTs; Mg^{2+}; Ca^{2+}; BP; RR; HR; ECG (to exclude contraindications).
- During the CSCI, the following is suggested:
  - check BP, RR, HR, and sedation every *4 hours* during the initial 24 hours or after adjusting the dose
  - if there is no dose change after 24 hours, monitoring interval can be increased to every *6 hours*.
- Monitor for toxicity while checking the above parameters (e.g. paraesthesia around the mouth).
- Consider the need for repeat ECG, LFTs, and U&Es.
- Treatment should be titrated cautiously, such that the risk of adverse effects is low. If *mild* adverse effects (see *Adverse effects*, p. 400) develop, the CSCI should be discontinued. Once symptoms resolve, treatment can be restarted, but at a *lower* dose.

Dose

Must only be used under the instruction of a specialist in centres with appropriate monitoring facilities.

†*Refractory cancer pain*

- Varying administration schedules have been described. Some suggest an initial test dose prior to commencing a parenteral continuous infusion.
  - 50mg to 100mg (approximately 1mg/kg–3mg/kg) SUBCUT infusion over 30–60 minutes *or* IVI over 20–30 minutes.
  - Commence CSCI at a rate of:
    - 0.5–2mg/kg/hr[3] or
    - 50mg/hr[4] or
    - 0.5–1.5mg/kg/hr.[5]
- Once pain has been stabilized, a gradual dose reduction should be considered. Case reports describe continued use for 1–2 weeks, although some patients may require >2 months.[4]

†*Intractable pruritus associated with T-cell lymphoma*

- A small case series used initial doses by CSCI ranging from 0.12mg/kg/hr to 0.89mg/kg/hr, to a maximum dose range of 0.38–1.19mg/kg/hr.[2] The median duration of CSCI treatment was 6 days.

Dose adjustments

Elderly

- No adjustments are necessary. No specific guidance is available. Accumulation of lidocaine and the active metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) has been reported to

occur after prolonged continuous infusion (e.g. 10 days), with marked reduction in clearance being associated with age, despite a low dose and normal renal and hepatic function. Therefore, a lower initial starting dose is suggested, e.g. 0.2mg/kg/hr or 250mg over 24 hours, and close monitoring is recommended.

Hepatic/renal impairment

- No specific guidance is available for use in patients with hepatic impairment. Nonetheless, in view of its hepatic metabolism, lower initial doses are suggested and dose requirements are carefully titrated.
- No specific guidance is available for patients with renal impairment, although the manufacturer suggests that dose modification is unnecessary. Nonetheless, lidocaine, MEGX, and GX are renally excreted, so a dose reduction may be considered with prolonged continuous infusion.

Additional information

- There does appear to be a specific plasma concentration of lidocaine above which pain relief may be achieved, reinforcing the need for individualizing therapy. It is suggested that lidocaine produces an 'all or nothing' analgesic response.
- Lidocaine via CSCI can be considered a therapeutic option either for severe pain that is unresponsive to usual pharmacological options or when the patient suffers intolerable adverse effects from these drugs. The first randomized, double-blind, placebo-controlled trial ($n = 33$) of lidocaine infusion by the SUBCUT route concluded that the blood level sufficient to have an analgesic effect may vary from one patient to another, even when dosing the infusion according to body weight.[6]

Pharmacology

The systemic analgesic effect of lidocaine is not fully understood, but it is believed to be multimodal in nature, although the primary clinically relevant target is believed to be voltage-gated Na^+ channels. At low doses of lidocaine, nerves in the spinal cord and dorsal root ganglion are particularly sensitive to the effects of lidocaine. Other mechanisms of action of parenteral lidocaine include enhancement of inhibitory descending pain pathways, inhibition of glycine receptors, release of endogenous opioids, and amelioration of NMDA-mediated nerve transmission.

Lidocaine is rapidly metabolized in the liver, producing the two active metabolites MEGX and GX; both are less active than the parent drug. *In vitro* studies suggest that CYP1A2 and CYP3A4 are involved. Lidocaine and its metabolites are renally excreted, with <10% excreted as unchanged drug. The average half-life of lidocaine in adults is 1.5–2 hours; however, it may be prolonged in patients receiving continuous parenteral lidocaine infusions. In adults with hepatic impairment, the half-life of lidocaine may reach values more than 2-fold greater than in healthy adults. Renal impairment can lead to accumulation of MEGX and GX; lidocaine is not removed by dialysis.

References

1. Lee JT, Sanderson CR, Xuan W, Agar M. Lidocaine for cancer pain in adults: a systematic review and meta-analysis. *J Palliat Med*. 2019;**22**(3):326–34.
2. Norris J, Barker J, Buelens O, Spruijt O. Does continuous subcutaneous infusion of lignocaine relieve intractable pruritus associated with advanced cutaneous T-cell lymphoma? A retrospective case series review. *Palliat Med*. 2019;**33**(5):552–6.
3. Ferrini R, Paice AJ. How to initiate and monitor infusional lidocaine for severe and/or neuropathic pain. *J Support Oncol.* 2004;**2**(1):90–4.
4. Chia SC, Hum A, Ong WY, Lee A. Parenteral lignocaine in cancer neuropathic pain: a series of case reports. *Prog Palliat Care*. 2014;**22**(5):253–7.
5. Seah DSE, Herschtal A, Tran H, Thakerar A, Fullerton S. Subcutaneous lidocaine infusion for pain in patients with cancer. *J Palliat Med*. 2017;**20**(6):667–71.
6. Hawley P, Fyles G, Jefferys SG. Subcutaneous lidocaine for cancer-related pain [published online ahead of print, 2020 Apr 27]. *J Palliat Med*. 2020;10.1089/jpm.2019.0621.

Lidocaine (topical) ⚠

Versatis® (POM)
Medicated plaster: 5% w/w lidocaine (700mg); 10cm × 14cm (30).

Ralvo® (POM)
Medicated plaster: 5% w/w lidocaine (700mg); 10cm × 14cm (30).

Unlicensed (POM)
Lidocaine hydrochloride BP 2% w/v in Lutrol® F127 24% w/v sterile gel (5mL).
See ➔ *Additional information*, p. 406.

Indications

- Symptomatic relief of neuropathic pain associated with post-herpetic neuralgia.
- †Post-thoracotomy pain.[1,2]
- †Post-mastectomy pain.[2]
- †There is developing experience that suggests that topical lidocaine may be useful in other localized neuropathies and musculoskeletal pain.[3]
- †Pain from malignant wounds (lidocaine 2% w/v in Lutrol® F127 24% gel—see ➔ *Additional information*, p. 406).[4]

Contraindications and cautions

- Contraindicated in patients with known hypersensitivity to lidocaine or other local anaesthetics of the amide type, e.g. bupivacaine.
- Do not apply to inflamed or broken skin, mucous membranes, or eyes.
- Although only 3 ± 2% of the total applied dose is systemically available, the manufacturer recommends that lidocaine plasters should be used with caution in patients with severe cardiac impairment, severe renal impairment, or severe hepatic impairment.

Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: administration site reactions (e.g. erythema, rash, pruritus).
- *Uncommon*: site injury (e.g. skin lesion).
- *Very rare*: anaphylaxis.

Drug interactions

Pharmacokinetic
- None have been reported. Given the low systemic absorption, it is unlikely that lidocaine plasters will be involved in pharmacokinetic interactions.

Pharmacodynamic
- Although none has been reported, lidocaine plasters may have an opioid-sparing effect, so regular review of analgesia requirements should be performed. The manufacturer states the plaster must be used with caution in patients receiving class I antiarrhythmic drugs and other local anaesthetics, as the risk of additive systemic effects cannot be excluded.

Dose

Neuropathic pain associated with post-herpetic neuralgia

- Apply up to three plasters over the affected area(s) for 12 hours, followed by a 12-hour plaster-free period.
- The plasters may be cut to size before removal of the backing material.
- Response to treatment can occur with application of the first plaster, but it may take up to 4 weeks for a response to occur. Treatment outcome should be reassessed after 2–4 weeks.

†Unlicensed indications

- Dose as above.
- Patches may be kept *in situ* for up to 18 hours if necessary.

Dose adjustments

Elderly

- No adjustments necessary.

Hepatic/renal impairment

- No adjustments are necessary, but the manufacturer recommends the plasters should be used with caution.

Additional information

- Do not refrigerate or freeze the plasters.
- Hair in the area where the plaster is to be applied should be cut with scissors prior to application. The area must not be shaved.
- After 12 hours, 650mg lidocaine remains in the plaster, so it must be disposed of carefully by folding the adhesive sides in half.
- Lidocaine hydrochloride BP 2% w/v in Lutrol® F127 24% w/v sterile gel can be used to treat pain from malignant wounds. It is an unlicensed product in the UK and is currently only obtainable from Oxford Pharmacy Store (https://oxfordpharmacystore.co.uk/).
  - Lutrol® gel is thermoreversible; the viscosity of the gel depends on the temperature. Viscosity increases rapidly with increasing temperatures, with a particularly rapid increase above 20°C; at body temperature, the gel almost solidifies. This makes it ideal as a wound barrier. It can be easily removed with warm water.
- The analgesic effect of Lutrol® gel with lidocaine 2% persists for between 6 and 8 hours. The product should be stored in a fridge for at least 30 minutes before use, allowing it to become runny. It can be poured from the bottle and spread over the affected area (one bottle will cover approximately 10cm^2).

Pharmacology

Lidocaine prevents the generation and conduction of nerve impulses by blocking Na^+ channels. As a general rule, small nerve fibres are more susceptible to the action of lidocaine than large fibres. C- and Aδ fibres that mediate pain and temperature are blocked before larger fibres that mediate, for example, touch and pressure (Aβ). Lidocaine binds more tightly and rapidly to open channels and it appears to preferentially inhibit abnormal excessive activity at ectopic foci with increased Na^+ channel density.

These conditions are present after peripheral nerve injury and in nociceptors sensitized by inflammatory modulators. The release characteristics of the lidocaine plaster are such that only very low concentrations penetrate the skin. Spontaneous ectopic discharges are suppressed by lidocaine applied topically and normal function is unaffected, i.e. the lidocaine plaster produces analgesia rather than anaesthesia.

References

1. Sansone P, Passavanti MB, Fiorelli A, *et al*. Efficacy of the topical 5% lidocaine medicated plaster in the treatment of chronic post-thoracotomy neuropathic pain. *Pain Manag*. 2017;**7**(3):189–96.
2. Hans G, Joukes E, Verhulst J, Vercauteren M. Management of neuropathic pain after surgical and non-surgical trauma with lidocaine 5% patches: study of 40 consecutive cases. *Curr Med Res Opin*. 2009;**25**(11):2737–43.
3. Amato F, Duse G, Consoletti L, *et al*. Efficacy and safety of 5% lidocaine-medicated plasters in localized pain with neuropathic and/or inflammatory characteristics: an observational, real-world study. *Eur Rev Med Pharmacol Sci*. 2017;**21**(18):4228–35.
4. Beynon T, Laverty D, Baxter A, Forsey P, Grocott P. Lutrol gel: a potential role in wounds? *J Pain Symptom Manage*. 2003;**26**(2):776–80.

Loperamide ♡

Imodium® (POM)
Capsule: 2mg (30).
Oral solution: 1mg/5mL (100mL).

Generic (POM)
Capsule: 2mg (30).
Tablet: 2mg (30).
NB—loperamide can be sold OTC, provided it is licensed and labelled for the treatment of acute diarrhoea and the maximum daily dose does not exceed 12mg.

Imodium® Instants (GSL)
Orodispersible tablet: 2mg (6; 12).

Generic (GSL/P)
Capsule: 2mg (6; 12).
Orodispersible tablet: 2mg (6).

Imodium® Instant Melts (P)
Orodispersible tablet: 2mg (12; 18).

Indications

- Acute diarrhoea.
- Chronic diarrhoea (*POM* only).

Contraindications and cautions

- Contraindicated for use in:
  - abdominal distension (discontinue if develops)
  - acute ulcerative colitis
  - antibiotic-associated colitis
  - ileus
  - toxic megacolon.
- There is a *conditional* risk of QT prolongation/TdP, with reported cases being linked with excessive daily dosages ranging from 40mg to 80mg, up to 800mg. Avoid concomitant administration of drugs that impair elimination (see ➔ *Drug interactions*, p. 409).
- If using doses greater than the recommended, use with caution in patients receiving CYP3A4 or P-gp inhibitors (see ➔ *Drug interactions*, p. 409).
- Avoid use of orodispersible tablets in patients with phenylketonuria; they contain aspartame, a source of phenylalanine.
- Use with caution in patients with hepatic impairment (risk of CNS toxicity).
- Patients with diarrhoea treated with loperamide may experience dizziness or drowsiness and should not drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: constipation; dizziness; flatulence; headache; nausea.
- *Uncommon*: abdominal pain; drowsiness; dry mouth; dyspepsia; rash; vomiting.

- *Rare*: abdominal bloating; angioedema; erythema multiforme; fatigue; miosis; paralytic ileus; pruritus; Stevens–Johnson syndrome; toxic epidermal necrolysis; urinary retention; urticaria.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Loperamide undergoes significant first-pass metabolism (CYP3A4) and it is a substrate of P-gp. Consequently, it has an oral bioavailability of approximately 0.3%. Loperamide is almost completely metabolized in the liver by CYP2C8 and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.
- The effect of grapefruit juice on the bioavailability of loperamide is unknown.
- Co-administration with P-gp inhibitors (e.g. *lansoprazole*, *quinidine*, *spironolactone*) may result in raised plasma levels. Although a drug interaction is unlikely to occur at therapeutic doses, the prescriber should be aware of the potential for interactions and that dose adjustments may be necessary.

Pharmacodynamic

- *Anticholinergic drugs*—additive constipating effects.
- *Erythromycin*—antagonism of anti-diarrhoeal effect.
- *Domperidone*—antagonism of anti-diarrhoeal effect.
- *Metoclopramide*—antagonism of anti-diarrhoeal effect.
- *Octreotide*—enhanced constipating effect.

Dose

Acute diarrhoea

- Initial dose 4mg PO, followed by 2mg PO after each loose stool. Maximum 16mg PO daily (*POM*) or 12mg PO daily (*GSL*).

Chronic diarrhoea

- Initial dose 4mg to 8mg PO daily in divided doses, adjusted to response. Maximum dose 16mg PO daily in two or more divided doses. ‡Higher doses (e.g. 32mg to 64mg PO daily in divided doses) may be necessary but should not be used if the patient is co-prescribed a CYP3A4 inhibitor (also use cautiously with P-gp inhibitors due to the risk of CNS opioid effects).

Dose adjustments

Elderly

- No dose adjustment is necessary.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. However, the manufacturer advises caution, given the extensive hepatic metabolism.
- No dose adjustment is necessary in renal impairment.

Pharmacology

Loperamide is a potent MOR agonist. It acts on MORs in the bowel, slowing intestinal motility and affecting water and electrolyte movement through the bowel. The net effect is a reduction of peristalsis and increase in intestinal transit time. Loperamide is almost completely metabolized in the liver by CYP2C8 and CYP3A4, usually resulting in very small, if not negligible, amounts entering the systemic circulation. The anti-diarrhoeal effect of loperamide may take between 16 to 24 hours to develop.

Lorazepam

Generic (CD4a POM)
Tablet: 1mg (28); 2.5mg (28).
NB—not all generic formulations are scored, so the prescriber should specify if a scored tablet is required.
Oral solution: 1mg/mL (150mL).
Injection: 4mg/mL.

Indications

- Anxiety (short term; 2–4 weeks).
- Insomnia (short term; 2–4 weeks).
- Status epilepticus (injection).
- †Dyspnoea (*second-line*).[1]

Contraindications and cautions

- Is contraindicated for use in patients with:
  - acute pulmonary insufficiency
  - myasthenia gravis
  - severe hepatic insufficiency (risk of hepatic encephalopathy)
  - sleep apnoea syndrome.
- A 50% dose reduction is recommended if co-prescribed with *sodium valproate* (see ➔ *Drug interactions*, p. 412).
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[2] The SmPC warns that concurrent use of lorazepam and opioids increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution if there is a history of drug or alcohol abuse.
- Lorazepam should be used with caution in patients with chronic respiratory disease, renal impairment, or moderate hepatic impairment.
- Dose reductions may be necessary in the elderly (see ➔ *Dose adjustments*, p. 413).
- Lorazepam is metabolized by glucuronidation via the enzyme UGT2B15 that is subject to polymorphism. One variant, found in 50% of the Caucasian population, has reduced activity, which should be considered if the patient has an unexpected augmented response (see ➔ *Pharmacology*, p. 413).
- Avoid abrupt withdrawal, even if short-duration treatment. Prolonged use of benzodiazepines may result in the development of dependence, with subsequent withdrawal symptoms on cessation of use, e.g. agitation, anxiety, confusion, headaches, restlessness, sleep disturbances, sweating, tremor. The risk of dependence increases with dose and duration of treatment. Gradual withdrawal is advised.

- Lorazepam may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: drowsiness.
- *Common*: asthenia; ataxia; dizziness; fatigue; muscle weakness.
- *Rare*: anterograde amnesia (transient); apnoea; constipation; headache; hypotension; impotence; jaundice; altered LFTs (increases in bilirubin, transaminases, and ALP); nausea; rash; respiratory depression; visual disturbances (blurred vision, diplopia).
- *Unknown*: aggressiveness; agitation; delusion; hallucinations; insomnia; irritability; nightmares; restlessness; sexual arousal.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- The metabolism of lorazepam does not involve the cytochrome P450 system, so pharmacokinetic interactions are likely to be minimal in comparison to other benzodiazepines. It is metabolized by glucuronidation via UGT2B4, UGT2B7, and UGT2B15 (major), which may be subject to drug–drug interactions that are yet to be identified.
- *Cannabidiol*—theoretical interaction as cannabidiol is a UGT2B7 inhibitor (more important in UGT2B15*2 variant).
- *Sodium valproate*—inhibits UGT2B15; a dose reduction of lorazepam by 50% is recommended.

Pharmacodynamic

- *Alcohol*—increased sedative effect and may precipitate seizures.
- *Antidepressants*—reduced seizure threshold.
- *Antipsychotics*—reduced seizure threshold.
- *CNS depressants*—additive sedative effect.
- *Opioids*—see *Contraindications and cautions*, p. 411.

Dose

Anxiety

- Initial dose 0.5mg to 1mg SUBLING^{+} or PO QDS PRN. Maximum dose of 4mg daily.

Insomnia

- 1mg to 2mg PO before bedtime.

Status epilepticus

- 4mg IV stat.
- The injection may be diluted 1:1 with NaCl or WFI immediately before administration into a large vein.
- The dose can be repeated once after a period of 10 minutes if necessary.

+Dyspnoea

- 0.5mg SUBLING PRN, to a maximum dose of 4mg daily.

Dose adjustments

Elderly

- No specific guidance is available. Use the lowest effective dose. For anxiety and dyspnoea, a maximum dose of 2mg/day PO/SUBLING is suggested; higher doses can be used after careful review.

Hepatic/renal impairment

- Contraindicated by the manufacturer in patients with severe hepatic impairment due to the risk of hepatic encephalopathy.
- No specific guidance is available for patients with mild/moderate hepatic or renal impairment. The dose of lorazepam must be carefully adjusted to individual requirements.

Additional information

- Although the injection has been administered via CSCI, this is generally not recommended because the formulation contains benzyl alcohol, polyethylene glycol, and propylene glycol; midazolam or clonazepam are the preferred choices.
- Tablets can be crushed and dispersed in water if necessary. A low volume of water can be used (e.g. ≤2mL).

Pharmacology

Lorazepam potentiates the action of GABA, resulting in increased neuronal inhibition and CNS depression, especially in limbic system and reticular formation. Metabolism of lorazepam is through direct glucuronide conjugation by UGT2B4, UGT2B7, and UGT2B15, avoiding the cytochrome P450 system. UGT2B15 is subject to genetic polymorphism and UGT2B15*2, a variant that results in reduced activity, is believed to be present in approximately 50% of Caucasians, with only a slightly lower prevalence in other populations. This may have clinical significance.

References

1. Simon ST, Higginson IJ, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev*. 2016;**10**:CD007354.
2. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.

Macrogol 3350

Movicol® (P)

Oral powder (lemon-lime; chocolate; plain): macrogol '3350', 13.125g, sodium bicarbonate 178.5mg, sodium chloride 350.7mg, potassium chloride 46.6mg/sachet (20; 30; 50).

Other brands include: CosmoCol®, Laxido®, Molative®, Vistaprep®.

Movicol Half®

Oral powder: macrogol '3350', 6.563g, sodium bicarbonate 89.3mg, sodium chloride 175.4mg, potassium chloride 23.3mg/sachet (20; 30).

Other brands include: CosmoCol Half®.

Movicol Liquid® (P)

Concentrate for oral solution (sugar-free; orange flavour): each 25mL contains macrogol '3350', 13.125g, sodium bicarbonate 178.5mg, sodium chloride 350.7mg, potassium chloride 46.6mg; *ethanol 74.5mg; benzyl alcohol 45.6mg* (500mL).

Movicol Ready to Take® (P)

Oral solution: *(strawberry-banana)*: each 25mL contains macrogol '3350', 13.125g, sodium bicarbonate 178.5mg, sodium chloride 350.7mg, potassium chloride 46.6mg (10; 30).

Indications

- Constipation.
- Faecal impaction (*not Movicol Liquid®*).

Contraindications and cautions

- Contraindicated for use in the following conditions:
  - Crohn's disease
  - ileus
  - intestinal perforation or obstruction
  - toxic megacolon
  - ulcerative colitis.
- There have been reports of aspiration and death after macrogol 3350 was mixed with a starch-based thickener. Addition of macrogol to a starch-based thickened liquid can produce a mixture that is thin and watery, thereby having the opposite effect. Patients with dysphagia who swallow the thinner liquid are potentially at greater risk of aspiration. The MHRA advises macrogol must not be directly mixed with a starch-based thickener, especially in patients with dysphagia who are considered at risk of aspiration such as elderly people and people with disabilities that affect swallowing.
- Patients with CV disease should not take >2 sachets in any 1 hour.
- The sodium content of each product should be considered before using in patients on a controlled sodium diet.
- *Movicol Liquid®* should not be used for the treatment of faecal impaction due to the high benzyl alcohol content.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- abdominal distension; abdominal pain; allergic reaction (e.g. dyspnoea, pruritus, urticaria); anal discomfort; borborygmi; diarrhoea; electrolyte disturbances; flatulence; headache; nausea; peripheral oedema; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Other medicines should not be taken orally for 1 hour before, and for 1 hour after, taking macrogol 3350 preparations due to the potential for increased or decreased absorption.
- *Starch-based thickeners*—see *Contraindications and cautions*, p. 414.

Pharmacodynamic

- *Anticholinergics*—antagonize the laxative effect.
- *Cyclizine*—antagonizes the laxative effect.
- *Opioids*—antagonize the laxative effect.
- *5-HT$_3$ antagonists*—antagonize the laxative effect.
- *TCAs*—antagonize the laxative effect.

Dose

The contents of each sachet of *oral powder* should be dissolved in 125mL of water. If *Movicol*® liquid is used, 25mL should be measured out using the dosing cup provided. This should be diluted in 100mL of water. *Movicol Ready to Take*® does not need additional dilution, although the manufacturer stipulates the patient should drink sufficient amounts of fluids (generally 2.0L to 2.5L daily) to maintain good health.

Constipation

- Usual dose one sachet per 25mL of oral solution OD to TDS.
- [+]The dose can be increased, if necessary, to up to two sachets TDS.

Faecal impaction

- Eight sachets (oral powder or *Movicol Ready to Take*®) to be taken within a 6-hour period.
- Patients with CV disease should not take >2 sachets in 1 hour.
- The dose can be repeated on days 2 and 3 if necessary.

Dose adjustments

Elderly

- No dose adjustment necessary.

Hepatic/renal impairment

- No specific dose adjustments are recommended by the manufacturers. However, given the electrolyte content, caution is advised in patients with significant renal impairment.

Additional information

- *Movicol Liquid*® contains 45.6mg of benzyl alcohol in each diluted dose of 125mL. The ADI of benzyl alcohol is 5mg/kg body weight. The maximum daily dose (25mL diluted in 100mL of water OD to TDS) should not be exceeded.
- After dilution of *Movicol Liquid*®, the solution should be used within 24 hours.
- After reconstitution of oral powder sachets, the solution should be kept in a refrigerator and discarded if unused after 6 hours.
- An effect should be seen within 1–3 days.

Pharmacology

Macrogol 3350 is a polyethylene glycol that produces an osmotic action in the gut, inducing a laxative effect. By increasing the volume of the stool, colon motility is stimulated, stools are softened, and defecation is facilitated.

Magnesium aspartate dihydrate

Magnaspartate® (GSL)
Oral powder: 6.5g (10mmolmg^{2+})/sachet (10).
Each sachet contains 2.706g of sucrose.

Indications

- Hypomagnesaemia.

Contraindications and cautions

- Contraindicated in severe renal impairment (GFR <30mL/min).
- Use with caution in patients with:
  - bradycardia
  - diabetes (sucrose content of product)
  - mild to moderate renal impairment—risk of hypermagnesaemia
  - severe dehydration
  - severe hepatic impairment (see ➔ *Dose adjustments*).

Adverse effects

- *Uncommon*: diarrhoea (following high dosage).
- *Very rare*: fatigue.
- *Unknown*: symptoms of hypermagnesaemia (e.g. nausea, vomiting, confusion, drowsiness).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Magnesium salts can influence the absorption of several drugs. An interval of at least 2–3 hours is suggested between *Magnaspartate®* and other drugs. The interval is recommended to be 3–4 hours in the case of certain drugs (e.g. bisphosphonates, iron, nitrofurantoin, penicillamine, quinidine).

Pharmacodynamic

- *Opioids*—risk of respiratory depression (associated with hypermagnesaemia).

Dose

- Initial dose 10mmol (one sachet) PO OD in 50mL to 200mL of water, tea, or orange juice, increasing to 10mmol PO BD if necessary. Higher doses will lead to the development of diarrhoea.

Dose adjustments

Elderly

- No specific dose adjustments recommended by the manufacturer.

Hepatic/renal impairment

- It should be used with caution in patients with severe hepatic impairment due to the possible risk of subsequent renal impairment.

- No dose adjustment is necessary for patients with mild to moderate renal impairment. *Magnaspartate®* is contraindicated for use in patients with severe renal impairment.

Additional information

- Low serum Mg^{2+} can cause secondary low serum Ca^{2+}, Na^{+}, and K^{+}.
- Compared with oral magnesium supplements, *Magnaspartate®* has excellent bioavailability.

Pharmacology

Magnaspartate® is a food supplement used in management of Mg^{2+} deficiency. Mg^{2+} is an essential electrolyte and involved in many enzyme systems. The largest body stores are found in bone. Magnesium salts are generally poorly absorbed orally, with the exception of *Magnaspartate®*, necessitating replacement therapy for symptomatic hypomagnesaemia by the IV route. Mg^{2+} is excreted renally and can accumulate in renal impairment.

Magnesium hydroxide

Generic (GSL)

Oral suspension: magnesium hydroxide, containing 415mg per 5mL (200mL; 500mL).

Indications

- Constipation.

Contraindications and cautions

- Contraindicated in acute GI conditions (e.g. acute inflammatory bowel diseases, abdominal pain of unknown origin, intestinal obstruction).
- Use with caution in patients with:
  - renal impairment—risk of hypermagnesaemia
  - severe dehydration
  - severe hepatic impairment (see *Dose adjustments*, p. 420).

Adverse effects

The frequency is not stated, but adverse effects include:

- diarrhoea; symptoms of hypermagnesaemia (e.g. nausea, vomiting, confusion, drowsiness).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Magnesium hydroxide should not be given within at least 1 hour of the following drugs/formulations:
  - *bisacodyl*—may remove the enteric coat and increase the risk of dyspepsia
  - *demeclocycline*—reduced absorption
  - *digoxin*—possible reduced absorption
  - *enteric-coated formulations*
  - *ferrous sulfate*—possible reduced absorption
  - *gabapentin*—reduced absorption
  - *lansoprazole*—reduced absorption
  - *paroxetine*—reduced absorption of suspension
  - *rabeprazole*—reduced absorption.

Pharmacodynamic

- *Anticholinergics*—antagonize the laxative effect.
- *Cyclizine*—antagonizes the laxative effect.
- *Opioids*—antagonize the laxative effect; risk of respiratory depression (associated with hypermagnesaemia).
- *5-HT$_3$ antagonists*—antagonize the laxative effect.
- *TCAs*—antagonize the laxative effect.

Dose

Antacid

- 5mL to10mL PO, as necessary, to a maximum of 60mL daily.

Laxative

- 30mL to 45mL PO at bedtime. May be taken with water if necessary.
- Occasionally used at a dose of 10mL to 20mL BD. Higher doses may be necessary (e.g. 30mL to 60mL BD).

Dose adjustments

Elderly

- No specific dose adjustments recommended by the manufacturer.

Hepatic/renal impairment

- No specific dose adjustments recommended by the manufacturer for patients with hepatic impairment. Nonetheless, use with caution in patients with severe hepatic impairment due the possible risk of subsequent renal impairment.
- Mg^{2+} can accumulate in patients with renal impairment. Use lower doses or choose an alternative.

Additional information

- Laxative effect can work within 1–6 hours, so administration times may need to be adjusted. Dose may need to be adjusted if co-administered with a stimulant laxative.

Pharmacology

Magnesium hydroxide has an indirect laxative effect caused by water retention in the intestinal lumen.

Magnesium sulfate

Generic (POM)
Magnesium sulfate 10% (100mg/mL; 0.4mmol/L).
Solution for infusion (amp): 1g/10mL (10).
Magnesium sulfate 50% (500mg/mL; 2mmol/L).
Solution for injection (amp): 1g/2mL (10); 2.5g/5mL (10); 5g/10mL (10); 10g/20mL (10).
Solution for infusion (amp): 25g/50mL (10).

Indications

- Symptomatic hypomagnesaemia.

Contraindications and cautions

- Contraindicated in severe renal impairment.
- Use with caution in patients with:
  - mild to moderate renal impairment—risk of hypermagnesaemia
  - myasthenia gravis
  - severe dehydration
  - severe hepatic impairment (see ➔ *Dose adjustments*).
- Serum Ca^{2+} levels should be routinely monitored in patients receiving magnesium sulfate.

☹ Adverse effects

The frequency is not stated, but adverse effects include:
- hypocalcaemia; symptoms of hypermagnesaemia (e.g. nausea, vomiting, confusion, drowsiness).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- None known.

Pharmacodynamic
- *Digoxin*—the manufacturer recommends caution with concomitant use.
- *Opioids*—risk of respiratory depression (associated with hypermagnesaemia).

Dose

- Up to 160mmol (40g) Mg^{2+} via slow IVI over up to 5 days may be required to replace the deficiency.
- Concentration of Mg^{2+} should not exceed 20% (200mg/mL or 0.8mmol/L); maximum rate of infusion is 150mg/min or 0.6mmol/min (i.e. 1.5mL/min of a 10% solution).
- Serum Mg^{2+} should be measured throughout treatment.
- Each centre should have its own policy. There are several suggested methods of replacement therapy:

- 35mmol to 50mmol (8.75g to 12.5g magnesium sulfate, or 17.5 mL to 25mL of 50% solution) diluted in 1L of NaCl or GLU via an infusion pump over 12–24 hours. Subsequent daily doses can be reviewed as per serum Mg^{2+}.
- 20mmol (5g magnesium sulfate, or 10mL of 50% solution) diluted in 1L of NaCl or GLU via an infusion pump over 3 hours. Subsequent daily doses can be reviewed as per serum Mg^{2+}.

Dose adjustments

Elderly

- No specific dose adjustments recommended by the manufacturer.

Hepatic/renal impairment

- No specific dose adjustments recommended by the manufacturer for patients with hepatic impairment. Nonetheless, it should be used with caution in patients with severe hepatic impairment due the possible risk of subsequent renal impairment.
- No specific dose adjustments recommended by the manufacturer for patients with renal impairment. Mg^{2+} can accumulate in patients with renal impairment and doses should be reduced. Plasma Mg^{2+} concentrations should be monitored throughout therapy.

Additional information

- To reduce venous irritation, IVI dilution to a concentration of up to 200mg/mL (or 0.8mmol/mL) is recommended.
- The administration rate should not exceed 150mg/min or 0.6mmol/min in order to avoid excessive renal losses.
- Low serum Mg^{2+} can cause secondary low serum Ca^{2+}, Na^{+}, and K^{+}.

Pharmacology

Mg^{2+} is an essential electrolyte and involved in many enzyme systems. The largest body stores are found in bone. Mg^{2+} salts are generally poorly absorbed orally, with the exception of *Magnaspartate®*, necessitating replacement therapy by the IV route. Mg^{2+} is excreted renally and can accumulate in renal impairment.

Medroxyprogesterone

Provera® (POM)
Tablet (scored): 2.5mg (30); 5mg (10; 100); 10mg (10; 90; 100); 100mg (60; 100); 200mg (30); 400mg (30).

Climanor® (POM)
Tablet: 5mg (28).

Indications

- Endometrial carcinoma.
- Renal cell carcinoma.
- Carcinoma of the breast in post-menopausal women.
- †Anorexia and cachexia.[1]
- †Sweating (associated with castration in men and women).[2,3]
- Dysfunctional (anovulatory) uterine bleeding (*not discussed*).
- Secondary amenorrhoea (*not discussed*).
- Endometriosis (mild to moderate) (*not discussed*).

Contraindications and cautions

- Medroxyprogesterone is contraindicated in patients with:
  - acute porphyria
  - angina
  - atherosclerosis
  - atrial fibrillation
  - cerebral infarction
  - DVT (current or previous)
  - endocarditis
  - heart failure
  - hypercalcaemia associated with bone metastases
  - impaired liver function or active liver disease
  - PE (current or previous)
  - suspected or early breast carcinoma
  - thromboembolic ischaemic attack (transient ischaemic attack)
  - thrombophlebitis
  - undiagnosed vaginal bleeding
  - valvular disorders.
- May cause hypercalcaemia in patients with breast cancer and bone metastases.
- Unexpected vaginal bleeding during treatment should be investigated.
- Treatment with medroxyprogesterone can cause Cushingoid symptoms.
- Discontinue treatment if the following develop:
  - jaundice or deterioration of liver function
  - significant increase in BP
  - new onset of migraine-type headache
  - sudden change in vision (partial or complete loss of vision, diplopia).
- Use with caution in patients with:
  - asthma
  - cardiac dysfunction

- continuous treatment with relatively large doses (monitor for signs of hypertension, Na^+ retention, and oedema)
- depression
- diabetes (impairment of glucose tolerance can occur)
- epilepsy
- hyperlipidaemia
- hypertension
- migraine
- renal impairment.

- Patients may experience dizziness or drowsiness with medroxyprogesterone and should not drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: increased appetite; constipation; dizziness; fatigue; headache; insomnia; hyperhidrosis; nausea; peripheral oedema; sexual dysfunction (erectile dysfunction); tremors; vomiting; weight fluctuation.
- *Uncommon*: acne; angioedema; congestive heart failure; depression; exacerbated diabetes mellitus; diarrhoea; dry mouth; hirsutism; hypercalcaemia; muscle spasm; PE; sexual dysfunction (loss of libido, dysfunctional uterine bleeding, breast pain); thrombophlebitis.
- *Rare*: alopecia; BP increase; cerebral infarction; drowsiness; hypersensitivity; jaundice; malaise; nervousness; pyrexia; rash; VTE.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Medroxyprogesterone is a substrate of CYP3A4. Despite this, the clearance of medroxyprogesterone is believed to be approximately equal to hepatic blood flow. Therefore, medroxyprogesterone would not be expected to be affected by drugs that alter hepatic enzyme activity.
- Nonetheless, co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of medroxyprogesterone through inhibition of intestinal CYP3A4.

Pharmacodynamic

- *NSAIDs*—increased risk of fluid retention.
- *Warfarin*—possible effect on bleeding times; INR should be monitored.

Dose

Endometrial and renal cell carcinoma

- 200mg to 600mg PO daily.

Breast carcinoma

- 400mg to 1500mg PO daily.

+Anorexia and cachexia

- Initial dose 400mg PO OM. Increase as necessary to a maximum of 1000mg PO daily (e.g. 500mg PO BD).

+Sweating

- 20mg PO OD to BD for at least 4 weeks, then reduce to the lowest possible dose that continues to relieve symptoms.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- The SmPC contraindicates the use of medroxyprogesterone in hepatic impairment or active liver disease.
- Although specific guidance is unavailable, the lowest effective dose should be used. Medroxyprogesterone should be used with caution in patients with renal impairment due to the risk of fluid retention (peripheral oedema).

Additional information

- As with corticosteroids and megestrol, the increase in body mass is likely to be due to retention of fluid or increase in body fat.
- Medroxyprogesterone has a catabolic effect on skeletal muscle, which could further weaken the patient.

Pharmacology

Medroxyprogesterone is a synthetic progestin and has the same physiological effects as natural progesterone. It has a similar effect to megestrol.

References

1. Madeddu C, Macciò A, Panzone F, Tanca FM, Mantovani G. Medroxyprogesterone acetate in the management of cancer cachexia. *Expert Opin Pharmacother*. 2009;**10**(8):1359–66.
2. Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol*. 2010; **11**(2):147–54.
3. Prior JC, Nielsen JD, Hitchcock CL, Williams LA. Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy. *Clin Sci*. 2007;**112**(10):517–25.

Megestrol

Megace® (POM)
Tablet (scored): 160mg (30).

Unlicensed special (POM)
Oral suspension: 40mg/5mL (150mL) (see *Additional information*, p. 427 for supply issues).

Indications

- Breast cancer.
- †Anorexia and cachexia.[1]
- †Sweating (in post-menopausal women and associated with castration in men).[2]

Contraindications and cautions

- Use with caution in patients with:
  - history of thrombophlebitis
  - severe impaired liver function.
- Glucose intolerance and Cushing's syndrome have been reported with the use of megestrol. The possibility of adrenal suppression should be considered in all patients taking, or withdrawing from, chronic megestrol treatment. Glucocorticoid replacement treatment may be necessary.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: adrenal insufficiency; increased appetite; constipation (associated with high doses); Cushing's syndrome; diabetes mellitus; dyspnoea; impaired glucose tolerance; hot flush; hyperglycaemia; hypertension; PE; thrombophlebitis; weight increase (the manufacturer states increase in fat and body cell mass, secondary to increased appetite).
- *Common*: alopecia; asthenia; carpal tunnel syndrome; diarrhoea; erectile dysfunction; flatulence; heart failure; lethargy; altered mood; nausea; oedema; pollakiuria (associated with high doses); rash; tumour flare (± hypercalcaemia); uterine bleeding (breakthrough); vomiting.
- *Uncommon*: urticaria.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is believed to be metabolized by CYP3A4/5 and metabolites further glucuronidated by UGTs, including UGT2B17. To date, no clinically significant pharmacokinetic interactions have been reported.

Pharmacodynamic

- None stated.

Dose

Breast cancer

- 160mg PO OD.

[+]Anorexia and cachexia

- Initial dose 160mg PO OD, increased as necessary up to 800mg daily in two or more divided doses. Treatment should be continued for at least 6 weeks.

[+]Sweating

- 20mg to 40mg PO OM. Assess response after 2–4 weeks.

Dose adjustments

Elderly

- The manufacturer states that there are insufficient data from clinical studies of megestrol in patients over the age of 65 to make specific recommendations. Clinical experience has not identified any issues, but megestrol is substantially excreted by the kidney; the risk of toxic reactions to this drug may be greater in patients with severe renal impairment. Elderly patients are more likely to have impaired renal function, making them more susceptible to adverse effects.

Hepatic/renal impairment

- Undergoes complete hepatic metabolism. Although specific guidance is unavailable, the lowest effective dose should be used. Megestrol is contraindicated in severe impaired liver function.
- Dose adjustments are not necessary in renal impairment, although the susceptibility to adverse effects may increase as renal function deteriorates.

Additional information

- Although an oral suspension is available as a special order, tablets can be crushed and dispersed in water immediately prior to administration.
- As with corticosteroids and medroxyprogesterone, the increase in body mass is likely to be due to retention of fluid or increase in body fat.
- Megestrol has a catabolic effect on skeletal muscle, which could further weaken the patient.

Pharmacology

Megestrol is a synthetic progestin and has the same physiological effects as natural progesterone. It interferes with the oestrogen cycle and suppresses luteinizing hormone release from the pituitary. It has a slight, but significant, glucocorticoid effect and a very slight mineralocorticoid effect. The precise mechanism of the effect on anorexia and cachexia is unknown. Megestrol has direct cytotoxic effects on breast cancer cells in tissue culture and may also have a direct effect on the endometrium.

References

1. Berenstein G, López-Briz E, Carbonell-Sanchis R, Bort-Martí S, Gonzálvez-Perales JL. Megestrol acetate for treatment of anorexia-cachexia syndrome. A systematic review. *J Cachexia Sarcopenia Muscle*. 2018;**9**(3):444–52.
2. Quella SK, Loprinzi CL, Sloan JA, *et al*. Long term use of megestrol acetate by cancer survivors for the treatment of hot flashes. *Cancer*. 1998;**82**(9):1784–8.

Metformin

Standard-release

Glucophage® (POM)
Tablet: 500mg (84); 850mg (56).

Generic (POM)
Tablet: 500mg (28; 84; 500); 850mg (56; 60; 300).
Oral solution (sugar-free): 500mg/5mL (100mL; 150mL).

Modified-release

Glucophage SR® (POM)
Tablet: 500mg (28; 56); 750mg (28; 56); 1000mg (28; 56).

Generic (POM)
Tablet: 500mg (28; 56); 750mg (28; 56); 1000mg (28; 56).

Indications

- Type 2 diabetes mellitus (particularly in overweight patients) not controlled by diet or exercise.
- Reduction in the risk, or delay of onset, of Type 2 diabetes mellitus.

Contraindications and cautions

- Do not use metformin in conditions that may increase the risk of developing lactic acidosis:
  - hepatic impairment
  - renal impairment where eGFR is <30mL/min/1.73m^2
  - severe congestive heart failure
  - severe COPD.
- Metformin must be discontinued prior to, and not restarted until, 48 hours post-administration of iodinated contrast agent.
- Discontinue metformin 48 hours prior to elective surgery requiring a general anaesthetic. Restart not less than 48 hours afterwards.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: tend to be GI in nature and can be reduced with slow titration or by ensuring the dose is taken during or after meals; they usually resolve spontaneously, e.g. diarrhoea, loss of appetite, nausea/vomiting.
- *Common*: taste disturbance (sometimes described as metallic), vitamin B12 deficiency (more likely to occur with high doses or after >3 years of use).
- *Very rare*: abnormal LFTs (usually reversible on discontinuation); lactic acidosis.

NB—hypoglycaemia does not occur with metformin unless there is a low carbohydrate intake.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Metformin is a substrate of the transport proteins OCT1 and OCT2. Drugs excreted by renal tubular secretion (e.g. amiloride, cefalexin, digoxin, morphine, quinine) have the potential to interact with metformin, increasing plasma concentrations. The clinical significance is unknown and until further information is available, the following is suggested:
  - if metformin is co-administered with these drugs, slow and cautious titration is advisable
  - if these drugs are prescribed for a patient already using metformin, it is advisable to review the metformin dose (lower doses may be required).
- Drugs which affect renal function have the potential to interact with metformin. If such drugs are co-administered, regular monitoring of renal function is advisable. Such drugs include:
  - ACE-Is; NSAIDs; iodinated contrast agent (see ➔ *Contraindications and cautions*, p. 428).

Pharmacodynamic

- Drugs that may precipitate hyperglycaemia may interfere with blood glucose control, e.g. corticosteroids, diuretics, nifedipine, olanzapine, risperidone.
- ACE-Is can cause hypoglycaemia via an unknown mechanism. Severe symptomatic cases have been reported when used in combination with antidiabetic drugs.
- Alcohol (increased risk of lactic acidosis with acute intoxication).

Dose

Standard-release

- Initial dose 500mg PO BD, with or after meals, and allow 1–2 weeks before increasing the dose. A slower titration improves GI tolerance.
- Dose increases of 500mg PO OD can be made at 1- to 2-weekly intervals to a maximum dose of 3g daily, in 2–3 divided doses, with or after meals.

Modified-release

- Initial dose 500mg PO OD with evening meal.
- Dose can be increased every 1–2 weeks by 500mg OD, to a maximum of 2g OD, with evening meal (or 1g BD, with meals, to improve blood glucose control).
- If blood glucose control is not achieved, change to standard-release formulations or review treatment.

Dose adjustments

Elderly

- Renal function must be assessed. Must not be used if eGFR is < 30mL/min.

Hepatic/renal impairment

- Avoid in hepatic impairment due to increased risk of lactic acidosis.
- Must not be used if eGFR <30mL/min/1.73m^2.

Additional information

- Metformin is occasionally combined with insulin to improve blood glucose control. Dose metformin as described above (see *Dose*, p. 429).
- In the absence of the oral solution, metformin tablets can be crushed and dispersed in water immediately prior to administration. The suspension can be flushed through a nasogastric tube.

Pharmacology

Metformin is a biguanide that delays the intestinal absorption of glucose, reduces hepatic glucose production (inhibits glycogenolysis and gluconeogenesis), and increases peripheral glucose uptake and utilization in muscle. It lowers basal and postprandial plasma glucose concentrations but does not stimulate insulin secretion (minimal risk of hypoglycaemia). The pharmacodynamics of metformin may rely upon a type of transport protein—the organic cation transporter (OCT). OCT1 is involved in the uptake of metformin by hepatocytes, whereas OCT2 is involved in renal excretion. Unexpected responses to metformin may be due to genetic polymorphisms in the *OCT1* and *OCT2* genes or by drug interactions (mainly with OCT2—see *Drug interactions*, p. 428). Metformin is excreted unchanged in the urine.

Methadone ⚠ ♥

Generic (CD2 POM)
Tablet: 5mg (50).
Injection: 10mg/mL (10); 50mg/mL (10).
Oral solution: 1mg/mL (various volumes).
NB—some generic formulations are sugar-free.
Oral concentrate: 10mg/mL (blue—150mL); 20mg/mL (brown—150mL).
NB—prescriptions should only be dispensed after appropriate dilution with Methadose® diluent.

Indications

- Moderate to severe pain (*NB—not all products are licensed for treatment of pain*).
- ⁺Adjunct to opioids[1,2] (see ➔ *Additional information*, p. 437).
- Treatment of opioid dependence (*not discussed*).

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care, although there may be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation). Nonetheless, the SmPC states that methadone is contraindicated for use in patients with:
  - head injury or raised intracranial pressure
  - obstructive airways disease (may cause histamine release)
  - paralytic ileus
  - respiratory depression.
- Concurrent administration with MAOIs, or within 2 weeks of their discontinuation, is contraindicated. If concomitant use is unavoidable (e.g. *linezolid*), ensure there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- Following a report of death by respiratory arrest with *clonazepam* and methadone among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[3] The SmPC warns that concurrent use of methadone and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 434). Of the opioids, *morphine* is believed to carry the lowest risk. Nonetheless, treatment must be reviewed urgently if symptoms develop, methadone

should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.

- There is a *known* risk of QT prolongation/TdP:
  - ECG monitoring is recommended before treatment with methadone if the patient has recognized risk factors for QT prolongation or is using concomitant drugs that may cause QT prolongation
  - avoid if QTc >500 ms; consider an alternative drug if QTc is between 450ms and 499ms (check for reversible causes of QT prolongation and reassess)
  - avoid concomitant administration of drugs that prolong the QT interval (see *Drug interactions*, p. 434)
  - avoid in patients with known QT prolongation or congenital long QT syndrome
  - correct electrolyte abnormalities (i.e. hypokalaemia, hypocalcaemia, and hypomagnesaemia) before commencing treatment
  - the SmPC recommends ECG monitoring before dose titration above 100mg/day and 7 days after titration
  - use with caution in patients with significant bradycardia, recent acute myocardial infarction, or uncompensated heart failure.
- Methadone has been associated with central and obstructive sleep apnoea, particularly as doses increase.
- A growing number of reports suggest methadone may cause hypoglycaemia in diabetic and non-diabetic patients. One study suggested the risk of hypoglycaemia is increased with doses >40mg/day. Nonetheless, it may be beneficial to monitor glucose levels when initiating methadone.[4,5] The SmPC recommends monitoring blood sugar during dose escalation.
- Use with caution in the following instances:
  - Addison's disease (adrenocortical insufficiency)
  - asthma (may cause histamine release)
  - cholecystectomy (risk of spasm of the sphincter of Oddi)
  - concurrent administration of drugs that have a potential for QT prolongation or are CYP3A4 and/or CYP2B6 inhibitors (see *Drug interactions*, p. 434)
  - diabetes (risk of hypoglycaemia)
  - diseases of the biliary tract; epilepsy (may lower seizure threshold)
  - hepatic impairment (risk of constipation and encephalopathy)
  - hypotension
  - hypothyroidism
  - inflammatory bowel disorders
  - myasthenia gravis
  - prostatic hypertrophy
  - renal impairment (if *sodium bicarbonate* is co-prescribed—see *Drug interactions*, p. 434)
  - sleep apnoea (respiratory effects of opioids are more pronounced during sleep).
- Methadone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

- Sudden cessation of tobacco smoking may lead to the development of adverse effects associated with excess dose (loss of CYP2B6 and CYP1A2 induction).
- Avoid abrupt withdrawal as the development of physical and/or psychological dependence can occur within 2 weeks of continual use. An abstinence syndrome may be precipitated if methadone is suddenly discontinued; it may occur within a few hours after withdrawal and is maximal between 1 and 3 days. Withdrawal symptoms include:
  - abdominal colic
  - anxiety
  - body aches
  - diarrhoea
  - dysphoria
  - flu-like symptoms
  - irritability
  - mydriasis
  - nausea
  - restless legs syndrome
  - tachycardia
  - tremors.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid. This is termed opioid-induced hyperalgesia (OIH). Pain associated with OIH tends to be more diffuse than the pre-existing pain and less defined in quality. The risk of developing OIH depends not only on the dose of opioid taken, but also on factors such as gender, age, genotype, and cause of pain, i.e. each case will be unique. Management of OIH can involve changing the opioid, a reduction in the dose (by 25–50%), and addition of non-opioid analgesics such as ketamine or pregabalin/gabapentin. Given the effect of methadone on the NMDA receptor, and noradrenaline and serotonin reuptake, the propensity for methadone to cause this effect, compared to other opioids, is unknown (see ➔, Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

☹ Adverse effects

Strong opioids tend to cause similar adverse effects, albeit to varying degrees. Refer to the SmPC for a full list of adverse effects.

- *Very common*: nausea; vomiting.
- *Common*: constipation; drowsiness; euphoria; fatigue; fluid retention; hallucinations; rash (transient); sweating; vertigo; visual disturbance (blurred vision); weight increase.

- *Uncommon*: agitation; asthenia; asthma (exacerbation); bile duct dyskinesia; dependence; disorientation; dry nose; dysphoria; glossitis; headache; hypotension; hypothermia; insomnia; pruritus; pulmonary oedema; respiratory depression (particularly with high doses), sexual dysfunction (e.g. amenorrhoea, decreased libido, erectile dysfunction); syncope; urinary retention; urticaria; xerostomia.
- *Rare*: bradycardia; palpitations, prolonged QT interval and TdP (associated with high doses).
- *Unknown*: hypoglycaemia; peripheral oedema.[6]

Drug interactions

Pharmacokinetic

- Methadone is a substrate of P-gp. It is metabolized by CYP2B6 and CYP3A4. To a lesser extent, CYP2C19, CYP2D6, and CYP1A2 are involved. Methadone may have a weak inhibitory effect on CYP2D6, UGT2B4, and UGT2B7. There is a suggestion that methadone induces its own metabolism. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Avoid grapefruit juice, as it may increase the bioavailability of methadone through inhibition of intestinal CYP3A4 and P-gp.
- *Amiodarone*—may increase plasma concentration of methadone.
- *Carbamazepine*—reduces the effect of methadone.
- *Ciprofloxacin*—may increase plasma concentration of methadone (especially in CYP2D6 poor metabolizers).
- *Clarithromycin*—may increase plasma concentration of methadone (also see ➔ *Pharmacodynamic*).
- *Clopidogrel*—may increase plasma concentration of methadone.
- *Erythromycin*—may increase plasma concentration of methadone.
- *Fluconazole*—may increase plasma concentration of methadone (although more likely to occur when fluconazole doses are >200mg daily).
- *Phenobarbital*—reduces the effect of methadone.
- *Sertraline*—may increase plasma concentration of methadone.
- *Sodium bicarbonate*—increases plasma concentration of methadone due to reduced renal excretion.
- Tobacco smoking may lead to faster metabolism of methadone. Dose adjustments may be necessary upon smoking cessation (see Box 1.11).

Pharmacodynamic

- Methadone can cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 431).

- Methadone is a weak serotonin uptake inhibitor; there is a risk of serotonin toxicity with:
  - *MAOIs* (see ➔ *Contraindications and cautions*, p. 431)
  - *MAO-B selective inhibitors* (*rasagiline*, *selegiline*)
  - *serotonergic drugs*—e.g. *mirtazapine*, *SNRIs*, *SSRIs*, *tapentadol*, *TCAs*, *tramadol*, *trazodone*.
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 431.
- *CNS depressants*—risk of excessive sedation.
- *Haloperidol*—may be an additive hypotensive effect (and an additive QT effect).
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of methadone may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect (and an additive QT effect).
- *Naloxegol*—in clinical trials, patients taking methadone had a higher frequency of GI adverse reactions (such as abdominal pain and diarrhoea), suggestive of opioid withdrawal.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 431.

Dose

Moderate to severe pain

Oral

Methadone should only be commenced in opioid-naïve patients by experienced practitioners.

Opioid-naïve[7]

- Initial dose should not exceed 7.5mg PO per day, e.g. 2.5mg PO TDS.
- Use lower initial doses in elderly or frail patients or in patients receiving CYP3A4/CYP2B6 inhibitors, e.g. 1mg PO BD.
- The dose should not be increased by >5mg/day or within 5–7 days of the dose increase (this allows for most patients to achieve steady state, although be aware that it may take longer in some patient populations, e.g. the elderly).

Previous opioid treatment[7,8]

Several methods exist. The reader is advised to follow local guidelines or policies. One example follows.

- Initial dose depends upon the patient's previous opioid requirements.
- This method involves a 5-day titration phase using an initial *loading dose*, followed by administration of a *fixed dose* of methadone 3-hourly PO PRN.
- If the patient is prescribed an alternative opioid, convert the total daily dose (e.g. PO oxycodone, transdermal fentanyl) to the equivalent PO

morphine dose (refer to *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences).

- The loading dose is calculated as *one-tenth* (10%) of the previous total daily morphine dose, to a *maximum of 30mg PO*.
- The fixed dose is calculated as *one-thirtieth* (3.3%) of the previous total daily morphine dose.
- For example:
  - 120mg/day PO oxycodone = 180mg/day PO morphine—loading dose of PO methadone = 18mg.
  - 120mg/day PO oxycodone = 180mg/day PO morphine—fixed dose of PO methadone = 6mg.

The procedure is as follows:

- Stop current opioid abruptly.
- If switching from *12-hourly* modified-release PO opioid:
  - if patient in pain—give the *loading dose* of methadone *6 hours* after the last PO opioid dose
  - if patient pain-free—give the *loading dose* of methadone *12 hours* after last PO opioid dose.
- If switching from *24-hourly* modified-release morphine:
  - if patient in pain—give the *loading dose* of methadone *12 hours* after last dose
  - if patient pain-free—give the *loading dose* of methadone *24 hours* after the last dose.
- If switching from transdermal fentanyl:
  - if patient in pain—give the *loading dose* of methadone *12 hours* after patch removal
  - if patient pain-free—give the *loading dose* of methadone *24 hours* after patch removal.
- Administer the *fixed dose* 3-hourly PRN for 5 days. If the patient experiences pain within 3 hours of the last PRN methadone dose, using the previously taken opioid, give a rescue dose (based on a dose of between 50% and 100% of the previously prescribed PRN dose). For example, if oxycodone was previously prescribed at 60mg BD prior to switching to methadone, the PRN dose to use for pain flares occurring within the 3-hour limit would be 10mg to 20mg PO oxycodone.
- On day 6, review the amount of methadone used in the preceding 48 hours (i.e. days 4 and 5). Divide this by *four* to arrive at a 12-hourly maintenance dose.
- Once a stable 12-hourly dose has been determined, future pain flares should *not* be treated with PRN methadone. This is mainly due to the risk of accumulation and the difficulty in determining the steady state. Pain flares should be managed with 10–15% of the previous daily opioid dose, every 2–4 hours. For example, if oxycodone was previously prescribed at 60mg BD prior to switching to methadone, a suitable PRN dose would be 15mg to 20mg, every 2–4 hours.
- The maintenance dose can be increased every 5–7 days if necessary (consider 10–14 days in the elderly).

Subcutaneous

- Methadone can be administered via SUBCUT injection or +CSCI, but it is rarely initiated in this way.
- Although the mean oral bioavailability is stated as 80%, the range varies from 41% to 99%, making the exact PO:SUBCUT equianalgesic equivalence ratio difficult to determine. When converting from the PO to SUBCUT route, a cautious approach using a ratio of 2:1 is often suggested, on the understanding that upward dose titration may be necessary. When converting from SUBCUT to PO, a ratio of 1:1 is suggested for similar reasons.
- Administration by SUBCUT injection (less so with CSCI) can cause some discomfort and may produce skin induration and erythema. Site rotation, dilution with saline (in the case of CSCI), and use of dexamethasone may overcome this.

+Adjunct to opioids[1,2]

- Typically, 0.5mg PO ON, increasing every 3–4 days, as necessary, to a usual maximum dose of 10mg PO ON.

Dose adjustments

Elderly

- No specific guidance is available; dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance is available, although in patients with hepatic impairment, the plasma concentration is expected to be increased. In view of its extensive protein binding (α_1 acid glycoprotein levels are reduced in liver disease) and hepatic metabolism, caution is advised when giving methadone to patients with hepatic impairment. Dose requirements should be individually titrated. Lower doses and extended intervals between dose adjustments (e.g. 10–14 days, rather than the usual 5–7 days) have been suggested for patients with advanced liver disease (Child–Pugh Class C).[7]
- No specific guidance is available for patients with renal impairment. The SmPC suggests that in moderate or severe renal impairment, dose reductions may be necessary. Dose requirements should be individually titrated. Recommendations for opioid use in renal impairment suggest a dose reduction of between 50% and 75% is necessary in patients with severe renal impairment.[9]

Additional information

- It is advisable to manage conversion from another opioid to methadone in an inpatient facility where close observation is possible. Consider obtaining an ECG prior to the initiation of methadone or following subsequent dose increases (if consistent with goals of care).
- Concentrated methadone oral solution is intended for dilution for the treatment of addiction but can be a useful preparation if high oral doses are required for pain. If being used in this way, it may be more convenient to dilute each dose individually.

- After administration sublingually, absorption of a single dose has been shown to be 35% (compare with fentanyl ≈ 54%). This route of administration also provides a rapid onset of action (average onset of action shown to be 5 minutes).[10]
- To reduce the incidence of CSCl site reactions, ensure the infusion is diluted maximally with NaCl. The addition of 1mg dexamethasone may improve tolerability, although check for compatibility. Changing to a 12-hourly infusion with site rotation may also help.
- Methadone is stated to be *physically* compatible under stated conditions with dexamethasone, haloperidol, hyoscine butylbromide, ketorolac, levomepromazine, metoclopramide, and midazolam.[11]

Pharmacology

Methadone is a synthetic opioid that is available commercially in the UK as the racemate, consisting of the laevorotatory and dextrorotatory enantiomers levomethadone (R (−) methadone) and dextromethadone (S (+) methadone), respectively. Levomethadone is responsible for the opioid activity of methadone, whereas dextromethadone has almost no opioid activity at normal therapeutic doses. Racemic methadone is a potent inhibitor of the reuptake of both noradrenaline and serotonin and has an affinity for the 5-HT_{2A} receptor. Both enantiomers also display similar NMDA antagonist properties, although at usual doses, this is not believed to be clinically significant.[12] Interestingly, methadone and tramadol share similar pharmacodynamic properties.

Methadone is a highly lipophilic drug with a large volume of distribution, leading to a prolonged half-life and risk of accumulation with repeated administration. When given orally, methadone has a mean bioavailability of 80% (range 39–100%). The absorption and bioavailability of methadone are likely to be affected by the activity of transport proteins (e.g. P-gp) and cytochrome activity (CYP3A4) in the GI mucosa. Both are susceptible to genetic variation, and concurrent drug treatment can also affect their activity. Methadone is highly bound to α_1 acid glycoprotein.

Metabolism to inactive metabolites occurs in the liver. There is some debate as to the predominant isoenzyme involved, as it was previously thought that CYP3A4 alone was mainly responsible, although CYP2B6 is now believed to have a significant role in the clearance of methadone. Stereoselective metabolism may occur; CYP2B6 may preferentially metabolize dextromethadone, whereas CYP2C19 may preferentially metabolize levomethadone. Other metabolic pathways with lesser involvement utilize CYP1A2 and CYP2D6, although they will become more important if they are induced (e.g. tobacco smoke induces both CYP2B6 and CYP1A2) or the patient is an ultrarapid metabolizer (CYP2D6). Genetic variations with respect to transport proteins (e.g. P-gp) and cytochrome P450 isoenzymes (e.g. CYP2B6) are believed to contribute to the large interpatient differences in the clinical pharmacology of methadone. Interestingly, CYP2C19 extensive metabolizers may have an increased risk of QT prolongation due to formation and accumulation of one of the metabolites.

Methadone has a long terminal half-life, ranging from 7 to 65 hours, with the time to steady state varying from 35 hours to 13.5 days. This long half-life has an important role in patients prescribed methadone. Firstly, there

is wide interpatient variation and accumulation can occur with continuous use. Consequently, the dose of methadone must be highly individualized. Secondly, with methadone toxicity, the long half-life will require naloxone administration either in repeated injections or in continuous infusion.

References

1. Chalker C, O'Neill H, Cranfield F. Efficacy of low-dose and/or adjuvant methadone in palliative medicine. *BMJ Support Palliat Care*. 2019. doi: 10.1136/bmjspcare-2018-001695.
2. Vu Bach T, Pan J, Kirstein A, Grief CJ, Grossman D. Use of methadone as an adjuvant medication to low-dose opioids for neuropathic pain in the frail elderly: a case series. *J Palliat Med*. 2016;**19**(12):1351–5.
3. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
4. Makunts T, Andrew U, Atayee RS, Abagyan R. Retrospective analysis reveals significant association of hypoglycemia with tramadol and methadone in contrast to other opioids. *Sci Rep*. 2019;**9**(1):12490.
5. Flory JH, Wiesenthal AC, Thaler HT, Koranteng L, Moryl N. Methadone use and the risk of hypoglycemia for inpatients with cancer pain. *J Pain Symptom Manage*. 2016;**51**(1):79–87.
6. Dawson C, Paterson F, McFatter F, Buchanan D. Methadone and oedema in the palliative care setting: a case report and review of the literature. *Scott Med J*. 2014;**59**(2):e11–13.
7. McPherson ML, Walker KA, Davis MP, *et al*. Safe and appropriate use of methadone in hospice and palliative care: expert consensus white paper. *J Pain Symptom Manage*. 2019;**57**(3):635–45.
8. McLean S, Twomey F. Methods of rotation from another strong opioid to methadone for the management of cancer pain: a systematic review of the available evidence. *J Pain Symptom Manage*. 2015;**50**(2):248–59.
9. Murtagh FE, Chai MO, Donohoe P, Edmonds PM, Higginson IJ. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. *J Pain Palliat Care Pharmacother*. 2007;**21**(2):5–16.
10. Gupta A, Duckles B, Giordano J. Use of sublingual methadone for treating pain of chemotherapy-induced oral mucositis. *J Opioid Manag*. 2010;**6**(1):67–9.
11. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.
12. Davis MP. Methadone does not block NMDA receptors. *J Pain Symptom Manage*. 2021;**62**(3):e7–8.

Methylnaltrexone

Relistor® (POM)
Injection: 20mg/mL (12mg/0.6mL vial).

Indications

- Treatment of OIC when response to laxative therapy has not been sufficient in adult patients aged 18 years and older.

Contraindications and cautions

- Must not be used in patients with known or suspected mechanical GI obstruction, patients at increased risk of recurrent obstruction, or patients with an acute surgical abdomen due to the potential for GI perforation.
- Should not be used for treatment of patients with constipation not related to opioid use.
- Administer with caution to patients with (not been studied):
  - colostomy
  - diverticular disease (active)
  - faecal impaction
  - peritoneal catheter.
- Administer with caution to patients with (from post-marketing reports of GI perforation):
  - diverticular disease
  - infiltrative GI tract malignancies
  - peptic ulcer disease
  - peritoneal metastases.
- A bowel movement can occur within 30–60 minutes of administration. Patients should be made aware and be in close proximity to toilet facilities.
- Treatment should not be continued beyond 4 months (treatment has not been studied in adult patients beyond this time).
- Not recommended in patients with severe hepatic impairment or end-stage renal impairment requiring dialysis (see *Dose adjustments*, p. 441).
- Symptoms of opioid withdrawal have been reported with methylnaltrexone. Patients with a suspected compromised blood–brain barrier are at risk of reduced analgesia and/or opioid withdrawal effects.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: abdominal pain; diarrhoea; flatulence; nausea.
- *Common*: dizziness; injection site reactions (e.g. stinging, burning, pain, redness, oedema); opioid withdrawal-like syndrome (abdominal pain, chills, hyperhidrosis, rhinorrhoea, tremor, vomiting).

Drug interactions

Pharmacokinetic

- Methylnaltrexone is a weak inhibitor of CYP2D6. It is unlikely to cause clinically significant interactions.

- Drugs excreted by renal tubular secretion (e.g. amiloride, digoxin, morphine, quinine) have the potential to interact with methylnaltrexone, increasing plasma concentrations. The clinical significance is unknown.

Pharmacodynamic

- While none have currently been observed, there is the theoretical risk that peripheral opioid analgesia will be antagonized.

Dose

Opioid-induced constipation in adult patients with chronic pain (except palliative care patients with advanced illness)

- 12mg (0.6mL) SUBCUT OD if required, given as 4 to 7 doses weekly.
- Treatment with usual laxatives should be *stopped* when commencing treatment with methylnaltrexone.

Opioid-induced constipation in adult patients with advanced illness (palliative care patients)

- For patients weighing 38–61kg, give 8mg (0.4mL) SUBCUT OD on alternate days.
- For patients weighing 62–114kg, give 12mg (0.6mL) SUBCUT OD on alternate days.
- Patients whose weight falls outside of these ranges should be dosed at 150 micrograms/kg SUBCUT OD on alternate days (or dose (mL) = patient weight (kg) × 0.0075).
- Doses may also be given with longer intervals, as per clinical need.
- Methylnaltrexone should be *added* to usual laxative treatment for this indication, and not replace it.
- Two consecutive doses, 24 hours apart, may be given if there is no response (i.e. no bowel movement) to treatment on the preceding day.

Dose adjustments

Elderly

- No dose adjustments are necessary based on age alone.

Hepatic/renal impairment

- No dose adjustments are necessary for patients with mild to moderate hepatic impairment. No data exist for use in patients with severe hepatic impairment and the SmPC states methylnaltrexone is not recommended.
- The SmPC states that in severe renal impairment (CrCl <30mL/min), the dose should be reduced to:
  - 8mg (0.4mL) for those whose weight is 62–114kg
  - 75 micrograms/kg for those whose weight falls outside of the 62–114kg range (round to a sensible dose, e.g. to the nearest 0.1mL).
- No information is currently available for patients with end-stage renal failure undergoing dialysis.

Additional information

- Initial response to treatment can produce abdominal pain, cramping, or colic. If severe, it can be managed by administration of an opioid or anticholinergic agent (e.g. morphine, glycopyrronium).

- Areas for injection include the upper legs, abdomen, and upper arms.
- Rotate the injection site.
- Avoid areas where the skin is tender, bruised, red, or hard. Scars or stretch marks should also be avoided.

Pharmacology

Methylnaltrexone is a quaternary amine selective MOR antagonist. It does not penetrate the blood–brain barrier to any significant extent because of its chemical structure. Opioid-mediated analgesic effects on the CNS are not affected by treatment with methylnaltrexone, provided the blood–brain barrier is not compromised.

Following SUBCUT administration, methylnaltrexone is rapidly absorbed, with peak concentrations achieved within 30 minutes. It does not affect the cytochrome P450 system to any significant degree, although it is a weak inhibitor of CYP2D6. Methylnaltrexone is primarily eliminated as the unchanged drug; approximately half of the dose is excreted in the urine.

Methylphenidate ⚠

Ritalin® (CD2 POM)

Tablet (scored): 10mg (30).

Modified-release preparations are available but are unsuitable for palliative care indications.

Generic (CD2 POM)

Tablet: 5mg (30); 10mg (30); 20mg (30).

Indications

- ⁺Depression.[1,2]
- ⁺Fatigue (associated with palliative care/cancer).[2-4]

Contraindications and cautions

- Concurrent use with an irreversible MAOI, or within 14 days of stopping one, is contraindicated due to the risk of a hypertensive crisis. Seek specialist advice if *linezolid* (a *reversible* MAO-A inhibitor) must be prescribed in a patient receiving methylphenidate.
- Methylphenidate is also contraindicated for use in patients with (refer to the SmPC for more details):
  - CV disorders (e.g. angina, heart failure, severe arrhythmias, severe hypertension)
  - glaucoma
  - hyperthyroidism
  - phaeochromocytoma
  - pre-existing cerebrovascular disorders
  - severe psychiatric disorder
  - thyrotoxicosis.
- The SmPC states that safety and efficacy have not yet been established in the elderly.
- Use with caution in patients with (refer to the SmPC for more details):
  - anxiety
  - concomitant medications that elevate BP
  - epilepsy (withdraw treatment if seizures occur)
  - motor tics, tics in siblings, or a family history or diagnosis of Tourette's syndrome.
- Patients who develop symptoms suggestive of cardiac disease (e.g. palpitations, exertional chest pain) during methylphenidate treatment should undergo a prompt specialist cardiac evaluation.
- After each dose adjustment and at least every 6 months thereafter, the following should be reviewed:
  - appetite
  - BP
  - psychiatric symptoms
  - pulse.
- Avoid abrupt withdrawal; symptoms such as fatigue, disturbed sleep patterns, and depression have been reported.
- If affected by drowsiness and dizziness, patients should be warned about driving. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: headache; insomnia (give last dose at no later than 2 p.m.); nervousness.
- *Common*: abdominal pain; aggression; agitation; alopecia; anorexia; anxiety; reduced appetite; arrhythmias; arthralgia; cough; depression; diarrhoea; dizziness; drowsiness; dry mouth; dyskinesia; hypertension; irritability; nasopharyngitis; nausea and vomiting (usually occurs during initiation; may improve if administered with food); palpitations; pharyngolaryngeal pain; pruritus; psychomotor hyperactivity; pyrexia; rash; tachycardia; urticaria.
- *Uncommon*: altered LFTs (raised); blurred vision; chest pain; constipation; diplopia; dyspnoea; hallucinations (auditory, visual, and tactile); haematuria; hypersensitivity reactions; altered mood (e.g. anger, mood swings); muscle twitching; myalgia; psychotic disorders; restlessness; sleep disorder; suicidal ideation; tics (or worsening of pre-existing); tremor.
- *Rare*: angina pectoris; convulsions; disorientation; gynaecomastia; hyperhidrosis; libido disorder; mania; NMS (other drugs taken concurrently; the exact role of methylphenidate is unclear); visual disturbances (e.g. mydriasis).
- *Unknown*: cerebrovascular disorders; confusional state; delusions; dependence; logorrhoea; migraine; pancytopenia; serotonin syndrome (see ➔ *Drug interactions*).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- It undergoes significant first-pass metabolism and the carboxylesterase CES1A1 is involved. Methylphenidate is not metabolized by the cytochrome P450 system to a clinically relevant extent.
- The SmPC reports that methylphenidate may inhibit the metabolism of *TCAs*, *SSRIs*, *phenytoin*, and *warfarin*. The mechanism remains unknown.

Pharmacodynamic

- *Anti-epileptics*—methylphenidate may antagonize the effects of anti-epileptics.
- *Antihypertensives*—effect may be reduced by methylphenidate.
- *Antidepressants*—may increase the risk of serotonin toxicity.
- *Cannabinoids*—may enhance the tachycardic effect (not cannabidiol).
- *Haloperidol*—reverses the wakefulness effect of methylphenidate (other dopamine antagonists may do the same).
- *MAOIs*—concurrent use is contraindicated (see ➔ *Contraindications and cautions*, p. 443).

Dose

BP should be monitored at appropriate intervals in all patients taking methylphenidate.

[+]Depression and fatigue

- Initial dose 2.5mg PO OM. Increase the dose by 2.5mg every 2–3 days, as tolerated. Doses above 2.5mg are usually divided, with the final dose being at no later than 2 pm. Usual maximum dose is 40mg PO daily.

Dose adjustments

Elderly

- The SmPC states there is no evidence in this cohort of patients and the drug should be avoided. There is no specific information available for use in the elderly and, if prescribed, use the lowest effective dose.

Hepatic/renal impairment

- There are no specific instructions for dose reduction in hepatic impairment. If the drug has to be used, the patient should be closely monitored and the lowest effective dose should be prescribed.
- There are no specific instructions for dose adjustment in renal impairment. However, since methylphenidate undergoes significant first-pass metabolism (to relatively inactive compounds), renal impairment is unlikely to have a great effect. Nonetheless, caution is advised and the lowest effective dose should be prescribed.

Additional information

- Methylphenidate can be cautiously combined with SSRIs in the treatment of resistant depression. It should be introduced slowly and the patient should be closely monitored.

Pharmacology

Methylphenidate is a mild CNS stimulant, with more prominent effects on mental than on motor activities. Its mode of action in humans is not completely understood, but it does block the dopamine reuptake transporter (DAT) and NET, increasing synaptic levels of both dopamine and noradrenaline. However, it does not appear to significantly affect SERT. Additionally, methylphenidate is an agonist at 5-HT_{1A} and α_2-adrenergic receptors.

References

1. Sood A, Barton DL, Loprinzi CL. Use of methylphenidate in patients with cancer. *Am J Hosp Palliat Care*. 2006;**23**(1):35–40.
2. Kerr CW, Drake J, Milch RA, *et al*. Effects of methylphenidate on fatigue and depression: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage*. 2012;**43**(1):68–77.
3. Mücke M, Mochamat, Cuhls H, *et al*. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev*. 2015;**5**:CD006788.
4. Tomlinson D, Robinson PD, Oberoi S, *et al*. Pharmacologic interventions for fatigue in cancer and transplantation: a meta-analysis. *Curr Oncol*. 2018;**25**(2):e152–67.

Metoclopramide ♡

Maxolon® (POM)

Tablet (scored): 10mg (84).
Syrup (sugar-free): 5mg/5mL (200mL).
Paediatric liquid (sugar-free): 1mg/mL (15mL).
Injection: 10mg/2mL (10).

Generic (POM)

Tablet (scored): 10mg (84).
Syrup (sugar-free): 5mg/5mL (200mL).
Injection: 10mg/2mL (10).

Indications

- Nausea and vomiting.
- †Hiccup.[1]
- Prevention of post-operative nausea and vomiting (*not discussed*).

Contraindications and cautions

- Contraindicated in patients with:
  - epilepsy (frequency and severity of seizures may increase)
  - GI obstruction, perforation, or haemorrhage
  - history of neuroleptic or metoclopramide-induced tardive dyskinesia
  - known history of methaemoglobinaemia with metoclopramide or of NADH cytochrome b5 deficiency
  - Parkinson's disease
  - phaeochromocytoma.
- Avoid within 4 days of GI surgery.

- The MHRA/CHM have issued safety advice concerning long-term use of metoclopramide for non-palliative care indications. A safety review concluded that the risk of potentially irreversible neurological effects, such as extrapyramidal disorders, outweighs the benefits in long-term or high-dose treatment. Consequently, metoclopramide should only be prescribed for a maximum duration of 5 days at a dose of 10mg PO/SUBCUT/IM/IV TDS.
- This advice does not apply to palliative care patients or patients with a limited prognosis, as the benefit of symptom control may outweigh the risk of possible adverse drug effects.

- There is a *conditional* risk of QT prolongation/TdP (particularly following IV administration):
  - avoid concomitant administration of drugs that prolong the QT interval (see ➲ *Drug interactions*, p. 447)
  - use with caution in patients with conditions where cardiac conduction is, or could be, impaired, with an increased risk of ventricular arrhythmia (e.g. congestive heart failure, QT prolongation)
  - correct significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) before commencing treatment.

- There is a risk of serotonin toxicity (see Chapter 1, *Serotonin toxicity*, p. 29) when metoclopramide is used concomitantly with certain drugs. Treatment should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Metoclopramide should be used cautiously with other drugs that display serotonergic effects (see *Drug interactions*).
- Use metoclopramide cautiously in the following situations:
  - concurrent use of serotonergic drugs and antipsychotics (see *Drug interactions*)
  - porphyria
  - severe renal and hepatic insufficiency (see *Dose adjustments*, p. 448).
- The elderly and young adults <20 years of age are more susceptible to adverse effects.
- Prolonged treatment with metoclopramide may cause tardive dyskinesia, which is potentially irreversible, especially in the elderly.
- CYP2D6 poor metabolizers or patients co-prescribed *strong* CYP2D6 inhibitors (see *Drug interactions*) may be more susceptible to adverse effects.
- Metoclopramide may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: somnolence.
- *Common*: akathisia; asthenia; depression; diarrhoea; extrapyramidal disorders; hypotension (especially IV administration); parkinsonism; restlessness.
- *Uncommon*: amenorrhoea; bradycardia (especially IV administration); dystonia (including oculogyric crisis and visual disturbances); hallucinations; hyperprolactinaemia; hypersensitivity.
- *Unknown*: anaphylaxis; atrioventricular block; cardiac arrest (shortly after injection and possibly subsequent to bradycardia); gynaecomastia; tardive dyskinesia; QT prolongation; tardive dyskinesia (especially in the elderly; may be irreversible); TdP.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Metoclopramide is metabolized by CYP2D6. Other cytochromes (e.g. CYP1A2, CYP2C9, CYP2C19, CYP3A4) have a minor role. Co-administration with drugs that are metabolized by, or inhibit the activity of, CYP2D6 (see *Cytochrome P450 tables* on the inside back cover) may lead to a clinically relevant drug interaction and the prescriber should be aware that dosage adjustments may be necessary.
- *Carbamazepine*—possible risk of neurotoxicity due to increased speed of absorption.
- *Digoxin*—metoclopramide *may* increase digoxin bioavailability.

- *Fluoxetine*—increased risk of adverse effects due to CYP2D6 inhibition.
- *Paracetamol*—potential increase in onset of analgesia.
- *Paroxetine*—increased risk of adverse effects due to CYP2D6 inhibition.

Pharmacodynamic

- Metoclopramide may cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *clarithromycin*, *citalopram*, *erythromycin*, *haloperidol*, *ondansetron*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 446). Refer to the SmPC for further details.
- *Serotonergic drugs*—caution is advisable if metoclopramide is co-administered with serotonergic drugs (e.g. *fentanyl*, *MAOIs*, *methadone*, *methylphenidate*, *mirtazapine*, *oxycodone*, *SNRIs*, *SSRIs*, *TCAs*, *tapentadol*, *tramadol*, *trazodone*) due to the risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29).
- *5-HT_3 antagonists*—antagonize the prokinetic effect.
- *Anticholinergics*—may antagonize the prokinetic effect.
- *Antipsychotics*—increased risk of extrapyramidal effects.
- *CNS depressants*—additive sedative effect.
- *Cyclizine*—may antagonize the prokinetic effect.
- *Levodopa and dopamine agonists*—effect antagonized by metoclopramide.
- *Opioids*—antagonize the prokinetic effect.
- *TCAs*—may antagonize the prokinetic effect.

Dose

Nausea and vomiting

- Initial dose 10mg PO/IM/IV/SUBCUT[+] TDS PRN. This can be increased to 20mg PO/SUBCUT TDS[+].
- Alternatively, 30mg via CSCI[+] over 24 hours. The dose can be increased to a maximum of 120mg via CSCI over 24 hours[+].

[+]Hiccup

- 10mg PO/SUBCUT TDS PRN.

Dose adjustments

Elderly

- The elderly are more susceptible to adverse effects. Therapy should be initiated at a reduced dose and then maintained at the lowest effective dose.

Hepatic/renal impairment

- Metoclopramide is metabolized in the liver and the predominant route of elimination of metoclopramide and its metabolites is via the kidney.
- The SmPC recommends that patients with severe hepatic impairment should have the dose reduced by 50%.
- In patients with moderate to severe renal impairment (CrCl 15 to 60mL/min), the SmPC recommends a dose reduction of 50%.
- In patients with end-stage renal disease (CrCl ≤15mL/min), the SmPC recommends a dose reduction of 75%.

Additional information

- Metoclopramide is *chemically and physically* compatible under stated conditions with alfentanil, diamorphine, hydromorphone, morphine hydrochloride, morphine sulfate, morphine tartrate, ondansetron, and oxycodone.[2]
- Under stated conditions, metoclopramide is *physically* compatible with dexamethasone, fentanyl, haloperidol, hyoscine butylbromide, methadone, midazolam, and tramadol.[2]

Pharmacology

Metoclopramide is primarily a D_2 antagonist. It also has serotonergic properties, being a 5-HT_3 antagonist and a 5-HT_4 agonist. The antiemetic action of metoclopramide results from its antagonist activity at D_2 receptors in the CTZ, making it a suitable choice for drug-induced causes of nausea/vomiting. At higher doses, the 5-HT_3 antagonist activity may also contribute to the antiemetic effect. D_2 antagonism in the GI tract enhances the response to acetylcholine, thereby indirectly increasing GI motility and accelerating gastric emptying; the 5-HT_4 agonist effect has a direct stimulatory effect on the bowel, enhancing the release of acetylcholine in the myenteric plexus, and both properties contribute to the prokinetic effect (which will, in turn, contribute to the antiemetic effect). D_2 antagonism can lead to increases in prolactin secretion, with consequences such as galactorrhoea, gynaecomastia, and irregular periods.

Metoclopramide is rapidly and almost completely absorbed from the GI tract after oral doses, although conditions such as vomiting or impaired gastric motility may reduce absorption. It is a substrate of CYP2D6, although many other cytochromes may also have minor roles (e.g. CYP1A2, CYP2C9, CYP2C19, CYP3A4). About 20–30% of the dose is excreted unchanged and plasma concentrations can increase in renal impairment.

References

1. Wang T, Wang D. Metoclopramide for patients with intractable hiccups: a multicentre, randomised, controlled pilot study. *Intern Med J*. 2014;**44**:1205–9.
2. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Miconazole (oral gel) ♡

Daktarin® (POM)
Oral gel (sugar-free): 20mg/mL (15g; 80g).
NB—the 15g tube (P) can be sold to the public.

Indications

- Treatment of candidosis of the oropharynx.

Contraindications and cautions

- Contraindicated for use in patients with hepatic dysfunction.
- The SmPC specifically contraindicates concurrent administration with the following drugs metabolized by CYP3A4 (refer to the SmPC for more details):
  - CYP3A4-metabolized substrates that can prolong the QT interval (e.g. domperidone, methadone)
  - ergot alkaloids
  - midazolam (oral)
  - HMG-CoA reductase inhibitors (e.g. simvastatin).
- There is a *conditional* risk of QT prolongation/TdP (CYP3A4 inhibition—see above)
- Miconazole is an inhibitor of other CYP enzymes (CYP2C9, in particular) and significant interactions *may* occur (see ➔ *Drug interactions*).
- Caution is required to ensure that the gel does not obstruct the throat because choking has been reported.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: dry mouth; nausea; oral discomfort; regurgitation; vomiting.
- *Uncommon*: dysgeusia.
- *Unknown*: diarrhoea (most likely with long-term treatment); hepatitis; rash; Stevens–Johnson syndrome; stomatitis; tongue discoloration; toxic epidermal necrolysis; urticaria.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Miconazole is a substrate of CYP3A4; it is an inhibitor of many cytochromes, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. The clinical significance is unknown, but the SmPC suggests caution with drugs metabolized by CYP2C9 and CYP3A4.
- Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Alfentanil*—may enhance the effect of alfentanil.

- *Apixaban*—may enhance the effect of apixaban.
- *Carbamazepine*—plasma concentration of carbamazepine may be increased.
- *Celecoxib*—plasma concentration of celecoxib may be increased.
- *Domperidone*—risk of prolonged QT interval due to increased domperidone plasma concentrations.
- *Edoxaban*—the effect of edoxaban may be enhanced.
- *Fentanyl*—may enhance the effect of fentanyl.
- *Methadone*—may enhance the effect of methadone; risk of prolonged QT interval.
- *Midazolam*—may enhance the effect of midazolam; risk of toxicity with oral midazolam.
- *Naloxegol*—risk of excessive exposure to naloxegol.
- *Oxycodone*—may enhance the effect of oxycodone.
- *Phenytoin*—increases the plasma concentrations of phenytoin; consider alternative treatment or closely monitor phenytoin plasma concentration.
- *Simvastatin*—risk of myopathy; avoid combination.
- *Sulfonylureas*—risk of hypoglycaemia; avoid combination.
- *Warfarin*—anticoagulant effect may be enhanced.

Pharmacodynamic

- None known.

Dose

- 2.5mL (50mg) PO QDS after food for up to 7 days after symptoms have resolved. Retain oral gel around lesion(s) for as long as possible before swallowing.

Dose adjustments

Elderly

- Normal doses can be used.

Hepatic/renal impairment

- The manufacturer contraindicates the use of miconazole in patients with hepatic dysfunction.
- Dose adjustments are unnecessary in patients with renal impairment.

Additional information

- Patients with dentures should remove them before using miconazole and clean them before reinsertion. Overnight, dentures should be removed and brushed with the gel.

Pharmacology

Miconazole is a broad-spectrum anti-fungal agent with antibacterial activity against certain Gram-positive bacteria. It produces an anti-fungal effect by inhibition of ergosterol biosynthesis in the cell membrane, changing the barrier function. Oral bioavailability of miconazole is absorbed systemically after administration as the oral gel. Most of absorbed miconazole is metabolized and <1% of a dose is excreted unchanged in the urine.

Midazolam

Hypnovel® (CD3 POM)
Injection: 10mg/2mL (10).

Buccolam® (CD3 POM)
Oromucosal solution (prefilled oral syringe): 10mg/2mL (4); 2.5mg/0.5mL (4); 5mg/mL (4); 7.5mg/1.5mL (4).

Epistasus® (CD3 POM)
Oromucosal solution (prefilled oral syringe): 10mg/mL (1).

Generic (CD3 POM)
Injection: 2mg/2mL (10); 5mg/5mL (10); 10mg/5mL (10); 10mg/2mL (10); 50mg/10mL (10).
Solution for infusion: 50mg/50mL (1); 100mg/50mL (1).

Indications

- †Dyspnoea.
- †Hiccups.
- †Major haemorrhage.
- †Myoclonus.
- †Seizures.
- †Status epilepticus.
- †Terminal agitation or anxiety.[1]

Contraindications and cautions

- Must not be used in patients with severe respiratory failure or acute respiratory depression. For end-of-life care, while the prescriber must consider these conditions, they should not necessarily be a deterrent to use, providing the dose is carefully titrated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[2] The SmPC warns that concurrent use of midazolam and opioids increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- The manufacturers of itraconazole and miconazole oral gel contraindicate co-administration with *oral* midazolam due to potential CYP3A4 interaction (see ➔ *Drug interactions*, p. 453).
- Use with caution in patients with:
  - cardiac disease
  - chronic respiratory insufficiency
  - myasthenia gravis (use low doses cautiously)
  - hepatic impairment and renal impairment (see ➔ *Dose adjustments*, p. 455).

- Prolonged treatment with midazolam can lead to the development of physical dependence. Abrupt cessation of treatment may precipitate withdrawal symptoms such as anxiety, confusion, convulsions, hallucinations, headaches, insomnia, and restlessness. Note such changes can occur after the introduction of a CYP3A4 inducer (see ➔ *Drug interactions*).
- Midazolam may modify reactions and, if appropriate, patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Given the manner in which midazolam is used in palliative care, the incidence of adverse effects is difficult to judge. Nonetheless, many adverse effects are dose-related. Refer to the SmPC for a full list of adverse effects for licensed indications. The frequency is not defined, but reported adverse effects include:

- anterograde amnesia; confusion; drowsiness; dry mouth; hiccups; nausea; paradoxical reactions (e.g. aggression, agitation, excitement, involuntary movements); rash; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Midazolam is a major substrate of CYP3A4/5. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Interactions with CYP3A4/5 inhibitors or inducers will be more pronounced for oral administration (compared to parenteral, buccal, or intranasal) because midazolam undergoes significant first pass metabolism.
- *Alfentanil*—may inhibit the metabolism of midazolam via competitive inhibition.
- *Aprepitant*—may significantly increase the effect of oral midazolam.
- *Carbamazepine*—reduces the plasma concentrations of midazolam (CYP3A4 induction); the dose of midazolam may need to be titrated accordingly if carbamazepine is added or discontinued.
- *Clarithromycin*—increased risk of midazolam toxicity, hence use lower initial doses; dose adjustments may be necessary if clarithromycin is added or discontinued.
- *Diltiazem*—increased risk of midazolam toxicity, hence use lower initial doses; dose adjustments may be necessary if diltiazem is added or discontinued.
- *Erythromycin*—increased risk of midazolam toxicity, hence use lower initial doses; dose adjustments may be necessary if erythromycin is added or discontinued.

- *Fentanyl*—may inhibit the metabolism of midazolam via competitive inhibition.
- *Fluconazole*—may inhibit the metabolism of midazolam (although more likely to occur when fluconazole doses are >200mg daily).
- *Grapefruit juice*—significantly increases the effect of midazolam administered PO; avoid concurrent use.
- *Itraconazole*—may significantly increase the effect of *oral* midazolam; the manufacturer of itraconazole contraindicates concurrent use.
- *Miconazole*—may significantly increase the effect of *oral* midazolam; the manufacturer of miconazole oral gel contraindicates concurrent use.

Pharmacodynamic

- *Alcohol*—may precipitate seizures and significantly increases the sedative effect of midazolam.
- *Antidepressants*—reduced seizure threshold.
- *Antipsychotics*—reduced seizure threshold.
- *CNS depressants*—additive sedative effect.
- *Opioids*—see *Contraindications and cautions*, p. 452.

Dose

+Dyspnoea (end-of-life care management)

- Dose should be titrated and adjusted to individual requirements.
- Typical initial dose is 2.5mg to 5mg SUBCUT PRN, or 5mg to 10mg via CSCI.
- Dose may be increased, if appropriate, to a maximum of 5mg to 10mg SUBCUT PRN, or 60mg via CSCI.
- Midazolam can be used as an adjunct to morphine for breathlessness.

+Hiccups (refractory)

- Dose should be titrated and adjusted to individual requirements.
- Initial dose 10mg via CSCI, increased if appropriate to a maximum of 60mg via CSCI.
- Note that midazolam is also implicated as a cause of hiccups.

+Major haemorrhage

- In the event of a catastrophic haemorrhage, remaining with the patient for the final moments is more appropriate.
- If drug treatment is appropriate, give 5mg to 10mg IV/IM/intranasal (see *Additional information*, p. 455 for intranasal administration), repeated every 10 minutes, if necessary, to a maximum dose of 30mg per episode.
- Avoid the SUBCUT route due to poor and erratic absorption.

+Myoclonus/seizures

- Dose should be titrated and adjusted to individual requirements.
- For prophylaxis in patients no longer able to manage oral anti-epileptics, a typical initial dose is 20mg to 30mg via CSCI, increasing if necessary to 60mg via CSCI.
- If the patient has not settled with 60mg midazolam via CSCI, an alternative treatment, such as phenobarbital, should be considered.
- Note that levetiracetam or sodium valproate via CSCI offer a less-sedating alternative treatment.

[+]Status epilepticus
- 10mg SUBCUT/IM/buccally/intranasal (see *Additional information* for intranasal administration).
- Dose may be repeated after 10–20 minutes if necessary. Further doses should not be given without medical assessment.

[+]Terminal agitation
- Ensure delirium is excluded prior to commencing midazolam (use of an antipsychotic, such as haloperidol, is preferred).
- Typical dose 2.5mg to 10mg SUBCUT PRN, or 10mg to 60mg via CSCI. The dose should be titrated and adjusted to individual requirements.
- If the patient has not settled with 30mg via CSCI, addition of an antipsychotic, such as levomepromazine, should be considered.

Dose adjustments

Elderly
- No specific guidance is available, but the dose should be carefully adjusted to individual requirements.

Hepatic/renal impairment
- In hepatic impairment, the SmPC suggests an empirical dose reduction due to a subsequent increase in terminal half-life.
- In patients with CrCl <10mL/min, a dose reduction should be considered due to an increased risk of sedation, as accumulation of an active metabolite can occur.

Additional information

- Although midazolam injection can be administered buccally[+], the volume may be too much for some patients.
- The injection may also be administered intranasally[+] (see *Dose*, p. 454) using a mucosal atomization device (MAD). This is available from SP Services. For further information regarding supply, see: https://www.spservices.co.uk/item/Brand_MAD300-MucosalAtomizationDevicewithLeurLock-Single_59_0_3560_1.html (accessed 23 April 2021).
- Midazolam is reportedly *chemically and physically* compatible in combination under stated conditions with alfentanil, diamorphine, fentanyl, haloperidol, hydromorphone, hyoscine butylbromide, morphine hydrochloride, morphine sulfate, ondansetron, and oxycodone. Under stated conditions, midazolam is reportedly *physically* compatible in combination with dihydrocodeine, methadone, metoclopramide, and tramadol.[3]
- Midazolam precipitates in solutions containing bicarbonate and it is likely to be unstable in solutions of alkaline pH (e.g. dexamethasone, ranitidine).

Pharmacology

Midazolam is a short-acting benzodiazepine, the exact mechanism of action of which is unknown, but it is believed to act as a modulator of the $GABA_A$ receptor, thereby enhancing GABA-ergic transmission in the CNS. It is extensively metabolized by CYP3A4 and CYP3A5; several metabolites are produced, which undergo glucuronidation and are renally excreted. The

CYP3A5 phenotype (usually inactive in the majority of Caucasians) may explain unexpected poor responses (see Box 1.3). One metabolite, 1′-hydroxymidazolam glucuronide, is active and contributes about 10% of the effect of IV midazolam. It can accumulate in renal impairment, leading to an increased risk of sedation.

References

1. Zaporowska-Stachowiak I, Szymański K, Oduah MT, Stachowiak-Szymczak K, Łuczak J, Sopata M. Midazolam: safety of use in palliative care: a systematic critical review. *Biomed Pharmacother*. 2019;**114**:108838.
2. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
3. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Mirtazapine ♀

Generic (POM)
Tablet: 15mg (28); 30mg (28); 45mg (28).
Orodispersible tablet: 15mg (30); 30mg (30); 45mg (30).
Oral solution: 15mg/mL (66mL bottle).

Indications

- Depression.
- ⁺Appetite.[1]
- ⁺Insomnia.[2]
- ⁺Pruritus.[3]

Contraindications and cautions

- Do not use with a MAOI or within 14 days of stopping one. At least 14 days should elapse after discontinuing mirtazapine treatment before starting a MAOI. The SmPC states that if *linezolid* must be administered with mirtazapine, the patient should be closely monitored for symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- There is a *possible* risk of QT prolongation/TdP (most reports are associated with overdose or involve other risk factors). Although such reports are currently absent from the SmPC's list of adverse effects:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 458)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- There is a risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when mirtazapine is used concomitantly with certain drugs. Treatment should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Mirtazapine should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 458). The SmPC states that serotonin syndrome occurs very rarely in patients treated with mirtazapine alone.
- Use with caution in:
  - diabetes (may alter glycaemic control)
  - elderly (greater risk of hyponatraemia)
  - epilepsy (may reduce the seizure threshold)
  - hepatic and renal impairment (see ➔ *Dose adjustments*, p. 460)
  - hypertension (see ➔ *Drug interactions*, p. 458)
  - hypotension (may cause postural hypotension).
- May precipitate akathisia/psychomotor restlessness, which usually appears during early treatment.
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.

- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- May precipitate psychomotor restlessness (e.g. akathisia, hyperkinesia), which usually appears during early treatment (consider discontinuing).
- Serious skin reactions (e.g. DRESS, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of mirtazapine. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with mirtazapine must not be restarted.
- Avoid abrupt withdrawal as symptoms such as loss of appetite, dizziness, agitation, anxiety, headache, nausea, and vomiting can occur. Mirtazapine should be withdrawn gradually over several weeks whenever possible. See ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- Avoid in patients with phenylketonuria—orodispersible tablets contain aspartame, a source of phenylalanine.
- Mirtazapine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Warn the patient about the importance of reporting signs of infection, such as sore throat and fever, during initial treatment (risk of agranulocytosis).

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: increased appetite (possible preference for carbohydrates); drowsiness (paradoxically improves as dose increases); dry mouth; headache; weight increase (≥7% body weight).
- *Common*: anxiety (may worsen during initial treatment); arthralgia; back pain; confusion; dizziness; dreams (abnormal); fatigue; insomnia (may occur during initial treatment); lethargy; peripheral oedema; postural hypotension; tremor.
- *Uncommon*: agitation; hallucinations; hypoaesthesia (oral); mania; nightmares; psychomotor restlessness; restless legs; syncope.
- *Rare*: aggression; elevated LFTs; myoclonus; pancreatitis.
- *Unknown*: bone marrow depression; convulsions; dysarthria; DRESS; erythema multiforme; hyponatraemia; hyperprolactinaemia (and related symptoms of galactorrhoea and gynaecomastia); jaundice; increased salivation; serotonin syndrome; SIADH; somnambulism; Stevens–Johnson syndrome; suicidal thoughts (can also occur shortly after discontinuation); toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Mirtazapine is metabolized by CYP1A2, CYP2D6, and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Carbamazepine* and *phenytoin* can reduce mirtazapine levels by at least 50%.
- Dose adjustments may be necessary upon smoking cessation.
- The effect of grapefruit juice on the absorption of mirtazapine is unknown.

Pharmacodynamic

- Mirtazapine carries a *small* risk of dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 457).
- Risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) with:
  - *MAOIs* (see ➔ *Contraindications and cautions*, p. 457)
  - *MAO-B selective inhibitors (rasagiline*, *selegiline)*
  - *serotonergic drugs*—e.g. *methadone*, *SNRIs*, *SSRIs*, *TCAs*, *tapentadol*, *tramadol*, *trazodone*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antidiabetics*—impaired glycaemic control.
- *Antihypertensives*—may increase the risk of hypotension.
- *CNS depressants*—risk of excessive sedation.
- *SNRIs/SSRIs*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Warfarin*—may cause increase in INR.

Dose

Depression

- Initial dose 15mg PO ON.
- Adjust dose as clinically appropriate; review within 2–4 weeks and increase dose to a maximum of 45mg/day, as a single dose at bedtime or as two divided doses.

†Appetite/insomnia

- Initial dose 7.5mg to 15mg PO ON. Review dose within 1 week and increase as necessary to a maximum dose of 45mg/day, as a single dose at bedtime or as two divided doses.
- Patient may show improved response to a BD dosing schedule.

†Pruritus

- Initial dose 7.5mg to 15mg PO ON. Higher doses may be of no further benefit.

Dose adjustments

Elderly

- Initial dose as above.
- 7.5mg dose may be paradoxically more sedative.
- Adjust dose as clinically appropriate.

Hepatic/renal impairment

- Specific dose recommendations are not provided by the SmPC. Clearance is reduced in both moderate to severe renal and hepatic impairment.
- The prescriber must be aware that plasma levels may be raised in these patients, and must adjust treatment as clinically appropriate. The recommendation is to use low initial doses and monitor response (although bear in mind that lower doses are paradoxically more sedative).

Additional information

- Mirtazapine has been shown to have useful antiemetic activity. An initial dose of 15mg PO ON may provide some relief.[4,5]
- It has been reported to be of benefit in the management of chronic breathlessness. While there are currently insufficient data to recommend routine use, mirtazapine may be considered in refractory cases. An initial dose of 15mg PO ON is suggested.[6]
- Relief of insomnia and anxiety can start shortly after initiation of dosing, but in general, it begins to exert an antidepressant effect after 1–2 weeks of treatment.
- Weight gain is more likely in women; however, any benefit after 6 weeks' treatment is unlikely.
- Mirtazapine is more likely than SSRIs to cause dry mouth and drowsiness (except paroxetine).
- Orodispersible tablets may block feeding tubes; in such instances, the oral solution should be used.
- The degree of buccal or sublingual absorption from the orodispersible tablet is presently unknown.

Pharmacology

Mirtazapine is an antidepressant that is believed to produce its effect through presynaptic α_2-adrenoreceptor antagonism, increasing both central noradrenergic and serotonergic neurotransmission, and 5-HT_{2C} antagonism. Typical adverse effects displayed by SSRIs are prevented with mirtazapine through 5-HT_{2A} and 5-HT_3 antagonism. Mirtazapine is also an antagonist of the H_1 receptor. Antagonism of 5-HT_3 and H_1 receptors would be expected to produce an antiemetic effect.

It is rapidly absorbed after oral administration, with a bioavailability of approximately 50%. Mirtazapine is extensively metabolized (via CYP1A2, CYP2D6, and CYP3A4) and eliminated via the urine and faeces. One of the

metabolites has the same pharmacological profile as mirtazapine. At low doses, the H_1 antagonistic effect generally predominates, leading to sedation during initial treatment, which improves as the dose escalates.

References

1. Riechelmann RP, Burman D, Tannock IF, Rodin G, Zimmermann C. Phase II trial of mirtazapine for cancer-related cachexia and anorexia. *Am J Hosp Palliat Care*. 2010;**27**(2):106–10.
2. Cankurtaran ES, Ozalp E, Soygur H, *et al*. Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: superiority over imipramine. *Support Care Cancer*. 2008;**16**(11):1291–8.
3. Davis MP, Frandsen JL, Walsh D, Andresen S. Mirtazapine for pruritus. *J Pain Symptom Manage*. 2003;**25**(3):288–91.
4. Kast RE, Foley KF. Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT3 antagonists with good antinausea effects. *Eur J Cancer Care*. 2007;**16**(4):351–4.
5. Malamood M, Roberts A, Kataria R, Parkman HP, Schey R. Mirtazapine for symptom control in refractory gastroparesis. *Drug Des Devel Ther*. 2017;**11**:1035–41.
6. Lovell N, Bajwah S, Maddocks M, Wilcock A, Higginson IJ. Use of mirtazapine in patients with chronic breathlessness: a case series. *Palliat Med*. 2018;**32**(9):1518–21.

Modafinil ⚠

Provigil® (POM)
Tablet: 100mg (30); 200mg (30).

Generic (POM)
Tablet: 100mg (30); 200mg (30).

Indications

- Narcolepsy with or without cataplexy (*not discussed*).
- +Cancer-related fatigue.[1,2]

Contraindications and cautions

- In 2010, the EMA recommended that the use of modafinil should be restricted to treat only sleepiness associated with narcolepsy as the licensed indication.
- Serious skin rashes have been reported with the use of modafinil, occurring within 1–5 weeks after treatment initiation. *Treatment should be withdrawn immediately and not restarted.*
- Multi-organ hypersensitivity reactions can occur, usually manifesting soon after initiation. Refer to the SmPC for further details. *Treatment should be withdrawn immediately and not restarted.*

- Modafinil is contraindicated for use in patients with uncontrolled moderate to severe hypertension or with arrhythmia.
- Avoid in patients with left ventricular hypertrophy or cor pulmonale.
- Use with caution in patients with a history of psychosis, mania, depression, or substance/alcohol abuse. If psychotic symptoms develop, modafinil should be withdrawn immediately and not restarted.
- Modafinil is associated with CV adverse effects. The SmPC and MHRA recommend that a baseline ECG should be performed before treatment initiation. BP and HR should be regularly monitored in patients receiving modafinil. Modafinil should be discontinued in patients who develop arrhythmia or moderate to severe hypertension.
- Symptoms of aggression or hostile behaviour can be caused by treatment with modafinil. If such symptoms occur, or worsen, modafinil should be discontinued.
- Anxiety may worsen with modafinil. Patients with major anxiety should only receive modafinil under specialist supervision.
- Use with caution in patients with:
  - diabetes (may alter glycaemic control)
  - renal impairment (see ➔ *Dose adjustments*, p. 464).
- Modafinil may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: headache.

- *Common*: abdominal pain; abnormal LFTs (dose-related); abnormal thinking; anxiety; reduced appetite; asthenia; blurred vision; chest pain; confusion; constipation; depression; diarrhoea; dizziness; drowsiness; dry mouth; dyspepsia; insomnia; irritability; nausea; nervousness; palpitation; paraesthesia; tachycardia; vasodilation.
- *Uncommon*: abnormal dreams; abnormal ECG; aggression; agitation; allergic reaction (minor, e.g. rhinitis); amnesia; increased appetite; arrhythmia; arthralgia; asthma; bradycardia; cough; depersonalization; diabetes mellitus; dry eye; dysgeusia; dyskinesia; dysphagia; dyspnoea; emotional lability; eosinophilia; epistaxis; glossitis; hypercholesterolaemia; hyperglycaemia; hyperkinesia; hypertension/hypotension; hypertonia; hypoaesthesia; leucopenia; decreased libido; menstrual disorder; mouth ulcers; migraine; movement disorder; myalgia; peripheral oedema; pharyngitis; psychomotor hyperactivity; rash; reflux; sinusitis; sleep disorder; speech disorder; suicidal ideation; sweating; thirst; tremor; urinary frequency; vertigo; vomiting; weight changes (increase/decrease).
- *Rare*: hallucinations; mania; psychosis.
- *Unknown*: delusions; multi-organ hypersensitivity reactions (including anaphylaxis); serious skin reactions, e.g. Stevens–Johnson syndrome, toxic epidermal necrosis, DRESS (usually within first 5 weeks of treatment, with isolated cases occurring after prolonged treatment).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Modafinil is metabolized mainly by amide hydrolysis, with a lesser contribution by CYP3A4. Both modafinil and a metabolite (modafinil sulfone) are strong inhibitors of CYP2C19. It is a weak inhibitor of CYP2C9 and a weak inducer of CYP1A2, CYP2B6, and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- In patients who are CYP2D6-deficient (or taking inhibiting drugs), the metabolism of SSRIs and TCAs via CYP2C19 becomes more important. Consequently, lower doses of the antidepressants may be necessary in patients co-administered with modafinil.
- *Diazepam*—may need a dose reduction of diazepam (CYP2C19 inhibition).
- *Omeprazole*—may cause increased omeprazole concentrations (CYP2C19 inhibition).
- *Phenytoin*—the SmPC recommends plasma monitoring during concurrent use (possibly phenytoin toxicity).

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antidiabetics*—modafinil may alter glycaemic control.
- *Cannabinoids*—may enhance the tachycardic effect (not cannabidiol).

Dose

- 100mg PO OM initially, increasing to 200mg PO OM, if necessary, after 7 days.

Dose adjustments

Elderly

- Usual adult dosing described above can be used.

Hepatic/renal impairment

- The SmPC recommends using half of the usual adult dose in patients with severe hepatic impairment.
- The SmPC states there is inadequate experience to determine the safety and efficacy of modafinil in patients with renal impairment. Severe renal failure (CrCl up to 20mL/min) does not significantly affect the pharmacokinetics of modafinil; however, exposure to the inactive metabolite modafinil acid can increase up to 9-fold.

Additional information

- An effect should be seen within 2 hours of dosing, although it may take several days to achieve an optimal clinical response. If no effect is seen after 7–10 days, discontinue.
- Monitor BP and HR in hypertensive patients.
- Patients who complain of headaches may find that taking with or after food may ameliorate the symptom.
- Tablets are dispersible in water. If necessary, the tablets can be crushed and dispersed in water prior to use. The resulting solution can be flushed down a feeding tube.

Pharmacology

Modafinil inhibits dopamine reuptake by binding to DAT, albeit with low potency, which enhances tonic dopamine activity to promote wakefulness. It also has other effects, including α_1-adrenoceptor activation, enhanced release of serotonin, glutamate, and histamine, and inhibition of GABA release.

After oral administration, modafinil is readily absorbed, with peak plasma concentrations after 2–4 hours and steady state within 2–4 days. It is primarily eliminated via metabolism in the liver to inactive metabolites by amide hydrolysis, with a lesser contribution by CYP3A4. Less than 10% of a dose is excreted unchanged. Both modafinil and one of its metabolites modafinil sulfone are strong inhibitors of CYP2C19.

References

1. Jean-Pierre P, Morrow GR, Roscoe JA, *et al*. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology Program Research base study. *Cancer*. 2010;**116**(14):3513–20.
2. Mücke M, Mochamat, Cuhls H, *et al*. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev*. 2015;**5**:CD006788.

Morphine

It is not possible to ensure the interchangeability of different makes of modified-release oral morphine preparations in individual patients. Therefore, it is recommended that patients should remain on the same product once treatment has been stabilized. Inclusion of the brand name on the prescription is suggested.

Standard-release oral products

Oramorph® oral solution (POM)
Solution: 10mg/5mL (100mL; 300mL; 500mL) (NB—discard 90 days after opening).

Oramorph® concentrated oral solution (CD2 POM)
Solution (sugar-free): 20mg/mL (30mL; 120mL) (*NB—discard 90 days after opening*).

Sevredol® (CD2 POM)
Tablet (scored): 10mg (*blue*—56); 20mg (*pink*—56); 50mg (*pale green*—56).

Actimorph® (CD2 POM)
Orodispersible tablet: 1mg (56); 2.5mg (56); 5mg (56); 10mg (56); 20mg (56); 30mg (56).

Generic (POM)
Solution: 10mg/5mL (100mL).

Standard-release rectal products

Generic (CD2 POM)
Suppository: 10mg (12); 15mg (12); 20mg (12); 30mg (12).
NB—products contain morphine sulfate or hydrochloride. Prescription must state the morphine salt to be dispensed.

Parenteral products

Generic (CD2 POM)
Injection: 10mg/mL; 15mg/mL; 20mg/mL; 30mg/mL—all in 1mL and 2mL amps.

12-hourly modified-release

Morphgesic® (CD2 POM)
Tablet: 10mg (*buff*—60); 30mg (*violet*—60); 60mg (*orange*—60); 100mg (*grey*—60).

MST Continus® (CD2 POM)
Tablet: 5mg (*white*—60); 10mg (*brown*—60); 15mg (*green*—60); 30mg (*purple*—60); 60mg (*orange*—60); 100mg (*grey*—60); 200mg (*green*—60).
Suspension (granules): 20mg (30); 30mg (30); 60mg (30); 100mg (30); 200mg (30).

Zomorph® (CD2 POM)
Capsule: 10mg (*yellow/clear*—60); 30mg (*pink/clear*—60); 60mg (*orange/clear*—60); 100mg (*white/clear*—60); 200mg (*clear*—60).

24-hourly modified-release

MXL® (CD2 POM)
Capsule: 30mg (*light blue*—28); 60mg (*brown*—28); 90mg (*pink*—28); 120mg (*green*—28); 150mg (*blue*—28); 200mg (*red-brown*—28).

Indications

- Relief of severe pain.
- †Relief of moderate pain.
- †Painful skin lesions (topical).[1,2]
- †Mucositis (topical).[1,2]
- †Cough.[3]
- †Dyspnoea.[4,5]

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care, although there may be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation). Nonetheless, the SmPC contraindicates morphine for use in patients with:
  - acute abdomen
  - acute hepatic impairment
  - head injury
  - obstructive airways disease
  - paralytic ileus
  - respiratory depression.
- The SmPC contraindicates concurrent administration with MAOIs or within 2 weeks of their discontinuation. If concomitant use is unavoidable (e.g. *linezolid*), ensure there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 468). Of the opioids, morphine is believed to carry the lowest risk. Nonetheless, treatment must be reviewed urgently if symptoms develop, morphine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[6] The SmPC warns that concurrent use of morphine and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution in the following instances:
  - acute alcoholism
  - Addison's disease (adrenocortical insufficiency)

  - asthma (morphine may release histamine)
  - biliary colic
  - cholecystectomy
  - COPD
  - convulsive disorders
  - delirium tremens
  - diseases of the biliary tract
  - elderly patients (see ➔ *Dose adjustments*, p. 471)
  - epilepsy (morphine may lower the seizure threshold)
  - head injury (risk of increased intracranial pressure)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 471)
  - history of alcohol and drug abuse
  - hypotension with hypovolaemia (morphine may result in severe hypotension)
  - hypothyroidism
  - inflammatory or obstructive bowel disorders
  - pancreatitis
  - prostatic hypertrophy
  - raised intracranial pressure
  - renal impairment (see ➔ *Dose adjustments*, p. 471)
  - sleep apnoea (respiratory effects of opioids are more pronounced during sleep)
  - ureteric colic.
- Morphine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Avoid abrupt withdrawal as the development of physical and/or psychological dependence can occur within 2 weeks of continual use. An abstinence syndrome may be precipitated if morphine is suddenly discontinued; it may occur within a few hours after withdrawal and is maximal between 1 and 3 days. Withdrawal symptoms include:
  - abdominal colic
  - anxiety
  - body aches
  - diarrhoea
  - dysphoria
  - flu-like symptoms
  - irritability
  - mydriasis
  - nausea
  - restless legs syndrome
  - tachycardia
  - tremors.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension,

and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid. This is termed opioid-induced hyperalgesia (OIH). Pain associated with OIH tends to be more diffuse than the pre-existing pain and less defined in quality. The risk of developing OIH depends not only on the dose of opioid taken, but also on factors such as gender, age, genotype, and cause of pain, i.e. each case will be unique. Management of OIH can involve changing the opioid, a reduction in the dose (by 25–50%), and addition of non-opioid analgesics such as ketamine or pregabalin/gabapentin.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. Strong opioids tend to cause similar adverse effects, albeit to varying degrees.
- *Very common*: constipation; nausea.
- *Common*: abdominal pain; anxiety; reduced appetite; asthenia; confusion; dizziness; dry mouth; fatigue; headache; hyperhidrosis; injection site reactions; insomnia; malaise; pruritus; rash; somnolence; vomiting.
- *Uncommon*: agitation; bronchospasm; convulsions; dysgeusia; dyspepsia; euphoria; flushing; hallucinations (auditory or visual); hypersensitivity; hypertonia; hypotension (including postural hypotension); increased LFTs; myoclonus (associated with toxicity); nightmares; palpitations; paraesthesia; paralytic ileus; peripheral oedema; pulmonary oedema; respiratory depression; syncope; tremor; urinary retention; urticaria; vertigo; visual disturbance.
- *Unknown*: allodynia (associated with toxicity); anaphylaxis; arrhythmias; biliary pain; dysphoria; hyperalgesia; hypertension; miosis; sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence); sensorineural hearing loss and tinnitus (associated with toxicity); tolerance; ureteric spasm.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Morphine is metabolized mainly by glucuronidation via several UGT enzymes, predominantly UGT2B7. Drugs that affect the activity of these (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) could influence the response to morphine, although the clinical significance is presently unknown. A minor pathway involves CYP2D6.
- Morphine is a substrate of P-gp and OCT1. Inhibitors of P-gp or OCT1 may alter the clinical effect of morphine, e.g. *itraconazole*, *spironolactone* (P-gp inhibitors), and may enhance the effect or morphine. The clinical significance of such interactions remains unknown.
- *Cannabidiol*—theoretical risk of increased morphine effects, as cannabidiol is a UGT2B7 inhibitor.

- Ketoconazole—possible risk of increased effect due to inhibition of UGT2B7.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see *Contraindications and cautions*, p. 466.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing affect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of morphine may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOIs*—risk of severe and unpredictable interactions with MAOIs, involving the potentiation of opioid or serotonergic effects.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see *Contraindications and cautions*, p. 466.

Dose

Note that it is generally accepted that PRN doses may be given every 2–4 hours (some centres suggest a maximum daily limit of six doses, irrespective of indication). In the case of severe pain or end-of-life care (e.g. pain, dyspnoea, cough), PRN doses may be given as frequently as every hour under specialist supervision.

Pain

The initial dose of morphine depends upon the patient's previous opioid requirements. Refer to *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences. Refer to *Breakthrough cancer pain*, p. 54 for guidance relating to BTcP.

Oral

Standard-release:

- For opioid-naïve patients, initial dose is 5mg to 10mg PO every 4–6 hours PRN (or more frequently, as described above). The dose is increased as necessary until a stable dose is attained. The patient should then be converted to a modified-release formulation. Lower initial doses are recommended for the elderly (see *Dose adjustments*, p. 471).
- †Lower initial doses, e.g. 2.5mg to 5mg PO every 4–6 hours PRN (or more frequently as described above), can be used for opioid-naïve patients to treat moderate pain (i.e. instead of using codeine).

Modified-release:

- For opioid-naïve patients, initial dose is 10mg PO BD. The dose can then be titrated, as necessary. Lower initial doses are recommended for the elderly (see *Dose adjustments*, p. 471).

- *MXL®* may be introduced once a total daily dose of 30mg or greater is reached.

Subcutaneous
- Initial dose in opioid-naïve patients is 2.5mg to 5mg SUBCUT every 4–6 hours PRN (or more frequently, as described above).
- Alternatively, 5mg to 10mg via CSCI over 24 hours and increase as necessary.
- The maximum dose per injection site that should be given by SUBCUT bolus injection is 60mg (= 2mL).

Rectal
- Initial dose 15mg to 30mg PR every 4 hours, adjusted according to response.

+Painful skin lesions
- Often use 0.1% or 0.125% w/w gels initially. These can be prepared immediately prior to administration by adding 10mg morphine injection to 8g Intrasite® gel (making a 0.125% w/w gel). Higher-strength gels, typically up to 0.5%, can be made if necessary.
- Initial dose: using a 0.125% gel (10mg morphine in 8g Intrasite® gel), apply 5mL to 10mL to the affected area at dressing changes (up to TDS). Rinse the wound with NaCl before reapplying the next dose.
- Use within 1 hour of preparation and discard any remaining product.

+Mucositis
- Often use 0.1% w/v initially. Preparations should be prepared immediately prior to administration by adding 10mg morphine injection to 10mL of a suitable carrier (e.g. Gelclair®, Oral Balance Gel®).
- Higher-strength preparations, up to 0.5% w/v, can be used if required.
- Initial dose: 10mg to the affected area BD to TDS.
- Use within 1 hour of preparation and discard any remaining product.

+Cough
- Standard release:
  - For opioid-naïve patients, initial dose 2.5mg PO every 4–6 hours and titrate the dose as necessary.
- Modified-release:
  - For opioid-naïve patients, initial dose 5mg PO BD and titrate the dose, as necessary.

+Dyspnoea
- In most cases, daily doses of up to 30mg PO (or 15mg SUBCUT) should be sufficient. Higher doses are rarely necessary (although may be needed for patients already established on opioid treatment).
- Standard release:
  - For opioid-naïve patients, suggested initial dose is 2.5mg PO every 4–6 hours and 2.5mg PO PRN every 2–4 hours.
  - In patients established on opioids, a dose that is equivalent to 25% of the current PRN rescue analgesic dose may be effective. This can be increased to up to 100% of the rescue dose in a graduated fashion if needed.

  - Alternatively, for opioid-naïve patients, initial dose is 1.25mg to 2.5mg SUBCUT PRN every 4 hours. If patients require >2 doses daily, use of a CSCI should be considered.
  - In patients established on opioids, a dose that is equivalent to 25% of the current PRN rescue analgesic dose may be effective. This can be increased to up to 100% of the rescue dose in a graduated fashion.
- Modified-release:
  - For opioid-naïve patients, 5mg PO BD with 1mg to 2.5mg PO PRN every 2–4 hours.

Dose adjustments

Elderly

- No specific guidance is available, although lower starting doses (e.g. 50%) in opioid-naïve patients are suggested. Dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance is available, although it is anticipated that plasma concentrations will rise in patients with hepatic impairment due to reduced metabolism, including first-pass metabolism. Caution is advised when giving morphine to patients with hepatic impairment. Lower starting doses in opioid-naïve patients are preferable and dose requirements should be individually titrated. Avoid modified-release formulations. Despite the UK SmPC contraindication, *hydromorphone* may be preferable to morphine.
- No specific guidance is available for patients with renal impairment. However, in view of the fact that the active metabolite morphine-6-glucuronide is renally excreted, lower starting doses in opioid-naïve patients may be preferable and dose requirements should be individually titrated. Alternatively, a different opioid may be more appropriate (e.g. *alfentanil*, *hydromorphone*, *oxycodone*, *fentanyl*).

Additional information

- If other analgesic measures are introduced—pharmacological or other alternatives, e.g. radiotherapy—the dose of morphine may need to be reduced.
- *Oramorph*® oral solution 10mg/5mL contains alcohol 10% v/v. It may cause stinging in patients with mucositis.
- *MXL*® and *Zomorph*® capsules should be swallowed whole, or the capsules can be opened and the contents sprinkled on soft food.
- Morphine sulfate is stated to be *chemically* and *physically* compatible under stated conditions with cyclizine, hyoscine butylbromide, hyoscine hydrobromide, ketamine, levomepromazine, metoclopramide, midazolam, and ondansetron. Under stated conditions, morphine sulfate is stated to be *physically* compatible with clonazepam, dexamethasone, furosemide, glycopyrronium, and ketorolac.[7]
- Morphine sulfate appears to show diluent and concentration-dependent compatibility with haloperidol.[7]

Pharmacology

Morphine is a strong opioid that interacts predominantly with the MOR. Following oral administration, morphine undergoes extensive first-pass metabolism, with bioavailability of approximately 30% but can range from between 10% and 65%. Absorption is rapid following a SUBCUT injection. The major pathway for morphine metabolism is glucuronidation, catalysed by UDP glucuronyltransferases (UGT2B7, in particular), in the liver and GI tract to produce morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The latter metabolite is considered to significantly contribute to the analgesic effect of morphine, whereas M3G is devoid of analgesic action and may even antagonize the action of morphine. Enterohepatic circulation of metabolites probably occurs, as up to 10% of a dose may be excreted in the bile. Approximately 60% of an oral dose and 90% of a parenteral dose are excreted renally within 24 hours.

References

1. Tran QN, Fancher T. Achieving analgesia for painful ulcers using topically applied morphine gel. *J Support Oncol*. 2007;**5**(6):289–93.
2. LeBon B, Zeppetella G, Higginson IJ. Effectiveness of topical administration of opioids in palliative care: a systematic review. *J Pain Symptom Manage*. 2009;**37**(5):913–17.
3. Wee B, Browning J, Adams A, *et al*. Management of chronic cough in patients receiving palliative care: review of evidence and recommendations by a task group of the Association for Palliative Medicine of Great Britain and Ireland. *Palliat Med*. 2012;**26**(6):780–7.
4. Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis. *Acta Oncol*. 2012;**51**(8):996–1008.
5. Verberkt CA, van den Beuken-van Everdingen MHJ, Schols JMGA, *et al*. Respiratory adverse effects of opioids for breathlessness: a systematic review and meta-analysis. *Eur Respir J*. 2017;**50**(5):1701153.
6. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
7. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Nabilone ⚠

Generic (CD2)
Capsule: 250 micrograms (20); 1mg (20).

Indications

- Chemotherapy-induced nausea and vomiting, unresponsive to conventional antiemetics.
- †Cancer pain.[1]
- †Cancer cachexia.[2]

Contraindications and cautions

- The SmPC states that nabilone is not to be used in patients where nausea and vomiting arise from any cause other than chemotherapy.
- Nabilone is not recommended for use in patients with severe hepatic dysfunction since it is excreted primarily by the biliary route.
- The SmPC states that patients, especially those who are treatment-naïve, should be closely observed within an inpatient setting due to the risk of serious untoward responses. Adverse psychiatric reactions can persist for 48–72 hours following cessation of treatment.
- Patients should be informed of the risk of changes in mood and other adverse behavioural effects that may occur.
- Use with caution in:
  - the elderly and those with heart disease due to the risk of tachycardia and postural hypotension
  - patients with current or previous psychiatric disorders (including manic depressive illness, depression, and schizophrenia).
- Withdrawal symptoms may develop if long-term treatment is stopped suddenly. Symptoms are usually mild and include anxiety, diaphoresis, diarrhoea, hiccups, hot flushes, insomnia, irritability, loss of appetite, and rhinorrhoea. A gradual, tapered withdrawal is recommended.
- Nabilone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency of adverse effects is not stated, but the most common reported adverse effects include (in decreasing order of incidence):

- drowsiness; vertigo/dizziness; euphoria; dry mouth; ataxia; visual disturbance; concentration difficulties; sleep disturbance; dysphoria; hypotension; headache; nausea.

Other less frequent adverse effects include:

- abdominal pain; decreased appetite; confusion; depression; disorientation; hallucinations; psychosis; tachycardia; tremors.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Nabilone is extensively metabolized by several pathways, including direct enzymatic activity (i.e. non-CYP) and a variety of CYP enzymes (e.g. CYP2C9, CYP3A4). *In vitro,* nabilone is a mild inhibitor of CYP3A4, and a moderate inhibitor of CYP2C8 and CYP2C9. The clinical relevance of the effect on these pathways has not been established; nonetheless, co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Note, however, that nabilone is unlikely to cause clinically significant inhibitory pharmacokinetic drug interactions at usual doses and associated low plasma concentrations.

Pharmacodynamic

- *CNS depressants*—risk of excessive sedation.
- *Opioids*—nabilone may potentiate the effects of opioids.
- *TCAs*—increased risk of hypertension, sedation, and tachycardia.

Dose

CINV

- Initial dose 1mg PO BD, increased if necessary to 2mg PO BD. The maximum daily dose is 2mg PO TDS.
- The first dose should be administered the night before initiation of chemotherapy, and the second dose should be given 1–3 hours before the first dose of the cytotoxic drug is administered.
- Nabilone should be continued, if necessary, for 48 hours after the last dose of each cycle.

†Cancer pain

- Note that evidence of a clear benefit is lacking.
- Nabilone should be started at a low dose and titrated slowly to effect.
- Initial dose 0.25mg to 0.5mg PO ON. Increase in increments of 0.5mg/week to a maximum daily dose of 6mg (2mg PO TDS).

†Cancer cachexia

- Note that evidence of a clear benefit is lacking.
- Initial dose 0.5mg PO ON, increasing to 1mg/day (single dose at night, or divided doses) after 1–2 weeks.

Dose adjustments

Elderly

- No specific dose recommendations are available. Use the lowest effective dose.

Hepatic/renal impairment

- No specific dose recommendations are available for hepatic impairment. The SmPC advises caution in severe impairment due to the primary method of excretion being biliary.

- No specific guidance is available for renal impairment. Roughly 25% of a dose is eliminated renally, so caution is advised in severe renal impairment.

Additional information

- The capsules can be opened, and the contents dispersed in water immediately before use.

Pharmacology

There are at least two types of CB receptor: CB_1 and CB_2. CB_1 receptors are found on pain pathways in the brain and spinal cord where they are thought to regulate cannabinoid-induced analgesia by attenuating the effects of excitatory neurotransmitters, e.g. glutamate. CB_1 receptors also affect cognition, memory, and motor function. CB_2 receptors have an effect on immune cells and may cause CBs to display anti-inflammatory effects. It is thought that the antiemetic effects of nabilone are mediated by CB_1 receptors that are located in the brain regions involved in the control of nausea and vomiting.

Nabilone is rapidly and almost completely absorbed when administrated orally. It is extensively metabolized, and several metabolites (some potentially active) have been identified. The pharmacological profile of these metabolites is unknown. Following oral administration, about 60% of nabilone and its metabolites are recovered in the faeces and about 24% in the urine, suggesting the major excretory pathway is the biliary system.

References

1. Tsang CC, Giudice MG. Nabilone for the management of pain. *Pharmacotherapy*. 2016;**36**(3):273–86.
2. Turcott JG, Del Rocío Guillen Núñez M, Flores-Estrada D, *et al*. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. *Support Care Cancer*. 2018;**26**(9):3029–38.

Nabumetone

Relifex® (POM)
Tablet: 500mg (60).

Generic (POM)
Tablet: 500mg (56).

Indications

- Pain and inflammation associated with osteoarthritis and rheumatoid arthritis.
- †Pain associated with cancer.[1,2]

Contraindications and cautions

- Contraindicated for use in patients with:
  - a history of peptic ulceration related to previous NSAID treatment
  - active, or a history of recurrent, peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
  - current cerebrovascular or other haemorrhage
  - hypersensitivity reactions to ibuprofen, aspirin, or other NSAIDs
  - severe heart, hepatic, or renal failure.
- Certain NSAIDs are associated with an increased risk of thrombotic events. There are presently insufficient data to exclude such a risk for nabumetone.
- Use the minimum effective dose for the shortest duration necessary in order to reduce the risk of CV and GI events. Treatment should be reviewed after 2 *weeks*. In the absence of benefit, other options should be considered.
- Elderly patients are more at risk of developing adverse effects.
- Use with caution in the following circumstances:
  - concurrent use of ACE-Is, ARBs, anticoagulants, antiplatelet drugs, diuretics, corticosteroids, and SSRIs (see ➔ *Drug interactions*, p. 477)
  - congestive heart failure
  - established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease (need careful consideration due to the increased risk of thrombotic events)
  - hepatic impairment
  - hypertension (particularly uncontrolled)
  - recovery from surgery
  - renal impairment
  - smoking (higher risk of CV and GI toxicity).
- Before initiating longer-term treatment, risk factors for CV disease should be considered (e.g. diabetes mellitus, hyperlipidaemia, hypertension, smoking).
- Patients taking long-term therapy need regular monitoring of renal and liver function.
- Abnormal LFTs can occur, which may be the result of hypersensitivity, rather than of direct toxicity. Nonetheless, discontinue NSAIDs if this persists.

- Nabumetone may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Consider co-prescription of misoprostol, PPI, or H_2 antagonist (usually reserved if PPI not possible) if at high risk of NSAID-induced GI toxicity, e.g. long-term NSAID therapy, concurrent use of drugs that increase the risk of GI toxicity (see ➔ *Drug interactions*).
- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of nabumetone. Patients appear to be at highest risk within the first month of treatment. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with nabumetone must not be restarted.
- Refer to ➔ Chapter 2, *Selection of an NSAID*, p. 49 for further information about selecting an NSAID.
- Nabumetone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; constipation; diarrhoea; dyspepsia; flatulence; gastritis; hypertension; nausea; oedema; pruritus; rash; tinnitus.
- *Uncommon*: altered LFTs; asthenia; confusion; dizziness; dry mouth; dyspnoea; epistaxis; fatigue; GI ulceration, bleeding, or perforation; headache; haematemesis; insomnia; melaena; myopathy; nervousness; paraesthesia; photosensitivity; somnolence; stomatitis; sweating; urinary tract disorder; urticaria; visual disturbances; vomiting.
- *Very rare*: alopecia; anaphylaxis; angioedema; GI ulceration; hepatic failure; interstitial pneumonitis; jaundice; leucopenia; increased LFTs; melaena; menorrhagia; oesophagitis; pancreatitis; photosensitivity; renal failure; Stevens–Johnson syndrome; thrombocytopenia; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Nabumetone is metabolized to the active metabolite 6-methoxy-2-naphthyl acetic acid (6-MNA). *In vitro* studies suggest CYP1A2 is involved. Metabolism of 6-MNA is believed to involve CYP2C9. Although there are presently no recognized clinically significant drug interactions, the prescriber should be aware that co-administration of CYP1A2 inhibitors or CYP2C9 inducers may reduce the effect of nabumetone. Co-administration of CYP1A2 inducers or CYP2C9 inhibitors may necessitate dosage adjustment.
- Dose adjustments may be necessary upon smoking cessation.
- *Digoxin*—monitoring of serum digoxin is recommended.
- *Methotrexate*—reduced excretion of methotrexate.

Pharmacodynamic

- *ACE-Is/ARBs*—risk of AKI.
- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—reduced hypotensive effect.
- *Antiplatelet drugs*—increased risk of bleeding; possible *reduced effect* of aspirin.
- *Corticosteroids*—increased risk of GI toxicity.
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Digoxin*—NSAIDs may exacerbate cardiac failure.
- *Diuretics*—increased risk of acute renal insufficiency (potential dehydration and/or hypovolaemia); nephrotoxicity of nabumetone may be increased.
- *Quinolone antibiotics*—risk of convulsions.
- *SSRIs*—increased risk of GI bleeding.
- *Trimethoprim*—increased risk of hyperkalaemia.

Dose

The dose should be taken preferably with or after food.

All indications

- Initial dose 1g PO ON. Dose can be increased, if necessary, to 500mg PO OM and 1g PO ON, followed by a further increase to 1g PO BD. Use the lowest effective dose and for the shortest duration possible.
- The SmPC states that patients should be monitored for GI bleeding for 4 weeks following initiation of therapy with nabumetone.

Dose adjustments

Elderly

- Initial dose 500mg PO ON, increased to a maximum of 1g PO ON. Use the lowest effective dose and for the shortest duration possible.

Hepatic/renal impairment

- Since the formation of the active metabolite depends on biotransformation in the liver, plasma concentrations could be decreased in patients with severe hepatic impairment; therefore, the manufacturer states that the drug should be used cautiously in such patients.
- Modification of nabumetone dose generally is not necessary in patients with mild renal impairment (CrCl ≥50mL/min).
- No specific guidance is available for use in patients with moderate to severe renal impairment. The SmPC states that in patients with moderate renal impairment (CrCl 30 to 49mL/min), there is a 50% increase in unbound plasma 6-MNA and a dose reduction may be warranted. In patients with severe renal impairment (CrCl <30mL/min), renal function should be performed at baseline and several weeks after initiating treatment. If renal function deteriorates, nabumetone should be discontinued.
- In all cases, use the lowest effective dose and for the shortest duration possible.

Pharmacology

Nabumetone is a pro-drug and has little pharmacological activity until it undergoes oxidation in the liver to form the active metabolite 6-MNA that is structurally similar to naproxen; 6-MNA is a relatively selective COX-2 inhibitor.

References

1. Derry S, Wiffen PJ, Moore RA, *et al*. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database Syst Rev*. 2017;**7**:CD012638.
2. Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. *Br J Anaesth*. 2019;**123**(2):e412–23.

Naldemedine

Rizmoic® (POM)
Tablet: 200 micrograms (28).

Indications

- Treatment of OIC in adult patients who have previously been treated with a laxative.
- Naldemedine is recommended by NICE as an option for treating OIC in adults who have had laxative treatment.[1]
- Refer to ➔ *Management of constipation in advanced cancer*, p. 64 for further information on management of constipation in advanced cancer.

Contraindications and cautions

- Contraindicated for use in patients with:
  - known or suspected GI obstruction or perforation
  - increased risk of recurrent obstruction, due to the potential for GI perforation.
- Naldemedine should be used with caution in the following situations:
  - CV disease—no data from clinical trials
  - conditions where the blood–brain barrier is disrupted (e.g. Alzheimer's disease—advanced, CNS metastases, multiple sclerosis—active, primary brain malignancies)—risk of opioid withdrawal
  - conditions with increased potential for GI perforation (e.g. Crohn's disease, diverticulitis, malignancy of the GI tract, severe peptic ulcer disease)
  - CYP3A4 inducers (see ➔ *Drug interactions*)
  - CYP3A4 inhibitors (mild—see ➔ *Drug interactions*)
  - severe hepatic impairment (see ➔ *Dose adjustments*, p. 481).

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: abdominal pain; diarrhoea; nausea; vomiting.
- *Uncommon*: opioid withdrawal syndrome.
- *Rare*: hypersensitivity.
- *Unknown*: GI perforation.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Naldemedine is a major substrate of CYP3A4/5; a minor pathway involves UGT1A3. It is also a substrate of P-gp. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.
- Co-administration with P-gp inhibitors (e.g. *lansoprazole*, *quinidine*, *spironolactone*) may result in raised plasma levels and consequent adverse effects.

- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of naldemedine through inhibition of intestinal CYP3A4.
- *CYP3A4 inhibitors (strong)*—concurrent use may increase exposure to naldemedine and risk of adverse effects.
- *CYP3A4 inhibitors (moderate)*—implication of interaction has not been established (compare with *naloxegol*).
- *CYP3A4 inducers (strong)*—concurrent use not recommended (reduced effect anticipated).

Pharmacodynamic
- *5-HT$_3$ antagonists*—antagonize the laxative effect.
- *Anticholinergics*—antagonize the laxative effect.
- *Corticosteroids*—may increase the risk of electrolyte imbalances.
- *Cyclizine*—antagonizes the laxative effect.
- *Diuretics*—may increase the risk of electrolyte imbalances.

Dose

- 200 micrograms PO OD, at any time of the day, but at the same time every day.
- May be used with or without laxatives.

Dose adjustments

Elderly
- Dosage adjustments are unnecessary.

Hepatic/renal impairment
- Dose adjustments are unnecessary for patients with mild to moderate hepatic impairment. The SmPC does not recommend the use of naloxegol in patients with severe hepatic impairment, due to lack of data.
- No dosage adjustment is required for patients with mild to moderate renal impairment. The SmPC recommends patients with severe renal impairment should be monitored during initiation, due to limited clinical experience.

Additional information

- There is limited experience in patients treated with opioids at daily doses of more than the equivalent of 400mg of PO morphine.
- There is no experience in patients treated for constipation induced by partial opioid μ-agonists (e.g. buprenorphine).
- Response to naldemedine usually occurs within 4–12 hours, with approximately two-thirds of patients responding within 24 hours.

Pharmacology

Naldemedine is a derivative of naltrexone that has been modified to reduce its permeability across the blood–brain barrier. It is also a substrate of P-gp, potentially further reducing penetration into the CNS. At recommended doses, naldemedine is unlikely to affect the analgesic effects of opioids. It acts as a peripherally acting MOR antagonist in the GI tract, reducing the constipating effects of opioids. Naldemedine is rapidly absorbed, with peak plasma concentrations occurring after 45 minutes. Food does

not affect absorption. It is highly protein-bound, mainly to serum albumin. Naldemedine is metabolized primarily by CYP3A4/5, with a minor pathway involving UGT1A3. Approximately 20% of a dose is excreted unchanged in the urine.

Reference

1. National Institute for Health and Care Excellence. Naldemedine for treating opioid-induced constipation. Technology appraisal guidance [TA651]. 2020. Available from: https://www.nice.org.uk/guidance/TA651. Accessed 9 April 2021.

Naloxegol ♡

Moventig® (POM)
Tablet: 12.5mg (30); 25mg (30).

Indications

- Treatment of OIC in adult patients who have had an inadequate response to laxative(s).

(Inadequate response is defined as: OIC symptoms of at least moderate severity in at least one of the four stool symptom domains (i.e. incomplete bowel movement, hard stools, straining or false alarms) while taking at least one laxative class for at least 4 days during the prior 2 weeks.)

- Naloxegol is recommended by NICE as an option for treating OIC in adults whose constipation has not adequately responded to laxatives.[1]
- Refer to ➔ *Management of constipation in advanced cancer*, p. 64 for further information on the management of constipation in advanced cancer.

Contraindications and cautions

- Contraindicated for use in patients with:
  - CYP3A4 inhibitors (strong, including grapefruit juice—see ➔ *Drug interactions*, p. 484); GI obstruction; ovarian cancer; underlying malignancies of the GI tract or peritoneum; vascular endothelial growth factor (VEGF) inhibitor treatment.
- Naloxegol should be used with caution in the following situations:
  - CV disease (although not mentioned by *CredibleMeds®*), e.g. myocardial infarction within previous 6 months, QT interval ≥500ms, symptomatic congestive heart failure
  - conditions where the blood–brain barrier is disrupted (e.g. Alzheimer's disease—advanced, CNS metastases, multiple sclerosis—active, primary brain malignancies)—risk of opioid withdrawal
  - conditions with increased potential for GI perforation (e.g. Crohn's disease, diverticulitis, severe peptic ulcer disease)
  - CYP3A4 inducers (see ➔ *Drug interactions*, p. 484)
  - CYP3A4 inhibitors (mild—see ➔ *Drug interactions*, p. 484)
  - hepatic impairment (severe—see ➔ *Dose adjustments*, p. 484)
  - renal impairment (severe—see ➔ *Dose adjustments*, p. 484).
- There is a risk of increased GI adverse reactions (e.g. abdominal pain, diarrhoea) in patients receiving methadone.
- If opioid withdrawal is suspected, naloxegol should be discontinued.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: abdominal pain; diarrhoea.
- *Common*: flatulence; headache; hyperhidrosis; nasopharyngitis; nausea; vomiting.
- *Uncommon*: opioid withdrawal syndrome.
- *Unknown*: hypersensitivity.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Naloxegol is a major substrate of CYP3A4/5. It is also a substrate of P-gp. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.
- Co-administration with P-gp inhibitors (e.g. *lansoprazole*, *quinidine*, *spironolactone*) may result in raised plasma levels under certain conditions (e.g. multiple P-gp inhibitors) and consequent adverse effects. P-gp inhibitors alone are unlikely to have a meaningful effect.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of naloxegol through inhibition of intestinal CYP3A4.
- *CYP3A4 inhibitors (strong)*—concurrent use is contraindicated (enhanced effect anticipated).
- *CYP3A4 inhibitors (moderate)*—see ➔ *Dose*.
- *CYP3A4 inducers (strong)*—concurrent use not recommended (reduced effect anticipated).

Pharmacodynamic

- *5-HT_3 antagonists*—antagonize the laxative effect.
- *Anticholinergics*—antagonize the laxative effect.
- *Corticosteroids*—may increase the risk of electrolyte imbalances.
- *Cyclizine*—antagonizes the laxative effect.
- *Diuretics*—may increase the risk of electrolyte imbalances.
- *Methadone*—in clinical trials, patients taking methadone had a higher frequency of GI adverse reactions (such as abdominal pain and diarrhoea), suggestive of opioid withdrawal.

Dose

- Laxatives should be discontinued until the effect of naloxegol is determined.
- 25mg PO OM, on an empty stomach at least 30 minutes prior to, or 2 hours after, the first meal of the day.
- If no or partial response after 48 hours, consider resuming laxatives.
- †The dose may be increased to 50mg PO OD if tolerated.
- *Patients taking moderate CYP3A4 inhibitors*: 12.5mg PO OD initially; increase to 25mg PO OM if necessary and tolerated.

Dose adjustments

Elderly

- Dosage adjustments are unnecessary.

Hepatic/renal impairment

- Dose adjustments are unnecessary for patients with mild to moderate hepatic impairment. The SmPC does not recommend the use of

naloxegol in patients with severe hepatic impairment, due to lack of data.
- No dosage adjustment is required for patients with mild renal impairment. For patients with moderate to severe renal impairment, the manufacturer recommends a starting dose of 12.5mg OD. If tolerated, increase to 25mg OD.

Additional information

- Response to naloxegol usually occurs within 6–12 hours, with two-thirds of patients responding within 24 hours.
- *Moventig*® can be crushed and mixed in approximately 120mL of water (i.e. half a glass) and drunk immediately. The container should be rinsed with a further 120mL, and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). The tube must be flushed thoroughly with water after administration of the mixture.
- If the patient experiences GI adverse effects, such as abdominal pain, diarrhoea, or nausea, consider reducing the dose to 12.5mg PO OD.

Pharmacology

Naloxegol is a pegylated derivative of naloxone that is a substrate for P-gp. Pegylation also reduces the passive permeability of naloxegol across the blood–brain barrier. At recommended doses, naloxegol is unlikely to affect the analgesic effects of opioids. It acts as a peripherally acting MOR antagonist in the GI tract, reducing the constipating effects of opioids. Naloxegol is rapidly absorbed after oral administration, with peak plasma concentrations occurring after 2 hours. A secondary plasma peak also occurs within an additional 3-hour period, most likely due to enterohepatic recirculation. Naloxegol is extensively metabolized by CYP3A4/5 and six metabolites have been identified; <6% of a total dose is excreted unchanged in the urine. The pharmacological activity of the metabolites at the opioid receptor is unknown.

Reference

1. National Institute for Health and Care Excellence. Naloxegol for treating opioid-induced constipation. Technology appraisal guidance [TA345]. 2015. Available from: https://www.nice.org.uk/guidance/ta345. Accessed 9 April 2021.

Naloxone

Generic (POM)
Injection (ampoule): 400 micrograms/mL.
Injection (prefilled syringe): 2mg/2mL.

Indications

- Treatment of opioid overdose (use only if the respiratory rate is <8 breaths/min, or <10–12 breaths/min and the patient is difficult to rouse and cyanosed).
- †Cholestatic pruritus.[1]

Contraindications and cautions

- No absolute contraindication when used for life-threatening respiratory depression.
- In opioid-dependent patients, administration of naloxone may precipitate acute withdrawal syndrome. Caution should be exercised when administered to patients with pre-existing CV problems and those with hepatic and renal impairment.
- Do not use to treat opioid-induced drowsiness.

Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: nausea.
- *Common*: dizziness; headache; hypertension; hypotension; tachycardia; vomiting.
- *Uncommon*: arrhythmia; bradycardia; diarrhoea; dry mouth; hyperventilation; local irritation and inflammation at the site of administration; sweating; tremor.
- *Rare*: seizures.
- *Very rare*: allergic reactions; anaphylaxis; cardiac arrest; erythema multiforme; fibrillation; pulmonary oedema.

Drug interactions

Pharmacokinetic
- None known.

Pharmacodynamic
- *Opioids*—antagonism of effects.

Dose

Reversal of opioid-induced respiratory depression (not life-threatening)
- *Follow local guidelines or policies*.
- The following is a suggested approach:
  - IV is the preferred route of administration for naloxone, but it can be given IM or SUBCUT if venous cannulation is not possible. The SmPC advises that recommended IV doses can be given by IM or SUBCUT injection. However, the pharmacokinetics of naloxone are subtly different by these routes, compared to IV, so slightly higher doses and increased frequencies are suggested.

- Administration of naloxone should be accompanied by other resuscitative measures such as administration of oxygen, mechanical ventilation, or artificial respiration.

By IV injection

- *Small* doses of naloxone by slow IV injection improve respiratory status without completely reversing opioid analgesia. Onset of action of IV naloxone is 1–2 minutes.
- Dilute a 400 micrograms/mL ampoule with 10mL of NaCl. Administer 40 micrograms to 80 micrograms (1mL to 2mL of diluted naloxone) as a slow IV bolus every 2 minutes until the patient's respiratory status is satisfactory (>8 breaths/min). *Do not titrate to the patient's level of consciousness.*

By IM or SUBCUT injection

- 100 micrograms (0.25mL of 400 micrograms/mL ampoule) of naloxone IM/SUBCUT should be given and repeated after 5 minutes if there is no improvement with the first dose.
- Patients usually respond after <200 micrograms with deeper breathing and an improved conscious level. Some patients may need 1mg to 2mg of naloxone.
- Closely monitor the respiratory rate and oxygen saturation (e.g. every 15 minutes for the first hour, then every 30 minutes for the next 4 hours). The length of this period of monitoring will be dependent on the half-life of the opioid causing toxicity.
- The duration of action of many opioids (e.g. modified-release formulations, methadone) exceeds that of naloxone (15–90 minutes) and impaired liver or renal function will slow clearance of the opioid. Depressant effects caused by the opioid may return as the effects of naloxone diminish, necessitating the administration of additional naloxone doses. At this point, a CIVI may be considered, or if venous cannulation is not possible, a CSCI. The following is a suggested approach:
  - calculate the dose requirement per hour by totalling the naloxone bolus doses and dividing by the time period over which all the doses have been given
  - start the IVI of naloxone at *half* this calculated hourly rate
  - adjust the naloxone infusion rate to keep the respiratory rate >8 breaths/min, and *do not titrate to the level of consciousness*
  - continue to monitor the patient closely (e.g. every 15 minutes for the first hour, then every 30 minutes for the next 4 hours). Continue the infusion until the patient's condition has stabilized (i.e. until the respiratory rate is at least >10 breaths/min).
- In the case of *buprenorphine* toxicity, standard doses of naloxone will not reverse the effects of overdose and higher doses, shown below, are necessary:
  - give IV naloxone 2mg injection over 90 seconds. Commence CIVI of naloxone at a rate of 4mg/hr until the patient's condition stabilizes (i.e. until the respiratory rate is at least >10 breaths/min). A CSCI may be used if venous cannulation is not possible.

+Cholestatic pruritus

- An initial IVI rate of very low-dose naloxone is suggested: 0.002 micrograms/kg/min (roughly 200 micrograms/24 hours for a 70kg patient). The dose can be gradually increased to a maximum of 0.2 micrograms/kg/min before switching to oral naltrexone (if appropriate).
- Administration of naloxone 0.4mg/hr by CSCI has been used successfully to manage cholestatic pruritus and reportedly did not reverse analgesia.

Dose adjustments

Elderly

- No specific guidance is available. The dose should be titrated to effect.

Hepatic/renal impairment

- No specific guidance is available. The dose should be titrated to effect. The SmPC advises caution and close monitoring of the patient.

Additional information

- To prepare an IVI for the reversal of opioid overdose, add 2mg of naloxone to 500mL of NaCl or GLU. The rate of administration should be titrated in accordance with the patient's response.
- Naloxone has an onset of action of 1–2 minutes by IV injection, and 2–5 minutes by SUBCUT/IM injection.

Pharmacology

Naloxone is an opioid antagonist, with a strong affinity for the MOR. It competes with, and displaces, opioids at receptor sites. It is rapidly metabolized by the liver, mainly via glucuronidation. Its effect lasts only 1–2 hours, explaining the need for repeated or prolonged administration when managing opioid excess.

Reference

1. Kumar N, Garg N, Bailey A. Opiate receptor antagonists for treatment of severe pruritus associated with advanced cholestatic liver disease. *J Palliat Med*. 2013;**16**(2):122–3.

Naproxen

Naprosyn® (POM)
Tablet (scored): 250mg (56); 500mg (56).

Naprosyn EC® (POM)
Tablet (e/c): 250mg (56); 375mg (56); 500mg (56).

Stirlescent® (POM)
Effervescent tablet: 250mg (20).

Generic (POM)
Tablet: 250mg (28; 56); 500mg (28; 56).
Tablet (e/c): 250mg (56); 375mg (56); 500mg (56).
Oral suspension: 25mg/mL (100mL); 50mg/mL (100mL).

With esomeprazole (see ➔ Chapter 3, *Esomeprazole, p. 256*).

Modified-release

Vimovo® (POM)
Tablet: naproxen 500mg, esomeprazole 20mg (60).
NB—naproxen 250mg e/c tablets (× 9) are available to purchase OTC.

Indications

- Pain and inflammation in musculoskeletal disorders.
- ✝Pain associated with cancer.[1,2]

Contraindications and cautions

- Contraindicated for use in patients with:
  - a history of peptic ulceration related to previous NSAID treatment
  - active, or history of recurrent, peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
  - current cerebrovascular or other haemorrhage
  - hypersensitivity reactions to ibuprofen, aspirin, or other NSAIDs
  - severe heart, hepatic, or renal failure.
- Use the minimum effective dose for the shortest duration necessary in order to reduce the risk of CV and GI events. Treatment should be reviewed after *2 weeks*. In the absence of benefit, other options should be considered.
- Elderly patients are more at risk of developing adverse effects.
- Avoid co-administration with low-dose aspirin.
  - Aspirin irreversibly inhibits platelet COX-1, but the plasma half-life of aspirin is short, being approximately 15–20 minutes. Naproxen, with a half-life of up to 17 hours, interferes with the binding of aspirin to platelet COX-1. Upon concurrent administration, the ensuing pharmacodynamic interaction prevents aspirin from irreversibly acetylating COX-1 and it is unlikely there will be any aspirin remaining in the circulation once naproxen has been released from the binding site. Nonetheless, regular dosing of 500mg BD of naproxen shows comparable antiplatelet effects of low-dose aspirin.
  - Notwithstanding the potential increased risk of GI toxicity, the clinical implications of the naproxen–aspirin interaction remain unclear.

- Use with caution in the following circumstances:
  - asthma (risk of bronchospasm)
  - atopy (risk of angioedema, bronchospasm, or urticaria)
  - concurrent use of diuretics, corticosteroids, and NSAIDs (see *Drug interactions*, p. 491)
  - mild to moderate congestive heart failure and/or left ventricular dysfunction
  - Crohn's disease
  - diabetes mellitus (may increase CV risk)
  - established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease (need careful consideration due to the increased risk of thrombotic events)
  - hepatic impairment
  - hyperlipidaemia (may increase CV risk)
  - hypertension (particularly uncontrolled)
  - recovery from surgery
  - renal impairment
  - rhinitis—chronic (risk of angioedema, bronchospasm, or urticaria)
  - smoking (higher risk of CV and GI toxicity)
  - ulcerative colitis.
- Before initiating longer-term treatment, risk factors for CV disease should be considered (e.g. diabetes mellitus, hyperlipidaemia, hypertension, smoking).
- Patients taking long-term therapy need regular monitoring of renal and liver function.
- Abnormal LFTs can occur, which may be the result of hypersensitivity, rather than of direct toxicity. Nonetheless, discontinue NSAID if this persists.
- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk within the first month of treatment. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with naproxen must not be restarted.
- Patients with SLE and mixed connective tissue disorders may be at risk of developing aseptic meningitis.
- Naproxen may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Consider co-prescription of misoprostol or a PPI if at high risk of NSAID-induced GI toxicity, e.g. long-term NSAID therapy, concurrent use of drugs that increase the risk of GI toxicity (see *Drug interactions*, p. 491).
- Refer to Chapter 2, *Selection of an NSAID*, p. 49 for further information about selecting an NSAID.
- Naproxen may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects (NB—there is some variation between SmPCs).

- *Very common*: abdominal pain (upper); constipation; diarrhoea; dyspepsia; nausea; vomiting.
- *Common*: agitation; cardiac failure exacerbation (dyspnoea, oedema); cognitive dysfunction; depression; dizziness; GI ulcer; headache; hyperhidrosis; insomnia; pruritus; rash; sleep disorders; thirst; tinnitus; urticaria; vertigo.
- *Uncommon*: alopecia; asthma exacerbation; bronchospasm; elevated LFTs; haematemesis; melaena; myalgia; photosensitivity; pyrexia (may be linked to haematological effects below); renal failure; stomatitis.
- *Very rare*: agranulocytosis; anaemia (aplastic, haemolytic); anaphylaxis; convulsions; aseptic meningitis (in patients with autoimmune disorders); hepatitis (with or without jaundice); hypersensitivity reactions (e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis); hypertension; hyperuricaemia; leucopenia; palpitations; pancytopenia; tachycardia; thrombocytopenia; vasculitis; visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- The principal route of elimination of naproxen is glucuronidation, mainly by UGT2B7, with UGT1A1, UGT1A3, UGT1A6, and UGT1A9 also contributing. Other metabolic pathways involve CYP1A2 and CYP2C9. Co-administration with drugs that are metabolized by, or affect the activity (see ➔ *Cytochrome P450 tables* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Cannabidiol*—inhibits UGT2B7, but the clinical significance is unknown.
- *Methotrexate*—reduced excretion of methotrexate.
- *Warfarin*—possible increased risk of bleeding through competitive inhibition of warfarin metabolism (5–11% of Caucasians have a variant of CYP2C9, requiring lower maintenance doses of warfarin; combination with naproxen may further reduce warfarin metabolism).

Pharmacodynamic

- *ACE-Is/ARBs*—risk of AKI.
- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—reduced antihypertensive effect.
- *Antiplatelet drugs*—increased risk of bleeding.
- *Aspirin (low dose)*—concomitant use should be avoided (see ➔ *Contraindications and cautions*, p. 489).
- *Corticosteroids*—increased risk of GI toxicity.
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Diuretics*—reduced diuretic effect; risk of AKI.
- *Quinolone antibiotics*—risk of convulsions.
- *SSRIs*—increased risk of GI bleeding.
- *Trimethoprim*—increased risk of hyperkalaemia.

Dose

Ensure gastroprotection (e.g. a PPI) is prescribed for patients at risk of NSAID-induced GI toxicity.

- Initial dose 500mg to 1000mg PO daily in 1–2 divided doses.
- *Naprosyn EC®* should be swallowed whole, whereas the other products should be taken with or after food.
- Maximum daily dose is 1250mg PO daily, which can be taken in 2–3 divided doses.
- For *Vimovo®*, the usual dose is one tablet PO BD.

Dose adjustments

Elderly

- Use the lowest effective dose and for the shortest duration possible.

Hepatic/renal impairment

- Naproxen is contraindicated for use in patients with severe hepatic or renal impairment.
- In hepatic impairment, no specific dose recommendations are available. However, the lowest dose possible should be used for the shortest duration possible.
- Naproxen should be used with extreme caution in renal impairment. Close monitoring of renal function is recommended. Naproxen is contraindicated for use in patients with CrCl <30mL/min.

Additional information

- If *Vimovo®* is used, ensure a PPI is not co-prescribed.
- It has been reported in several studies to be the NSAID with the lowest CV risk. Unlike low-dose aspirin, however, naproxen cannot be considered to be cardioprotective despite possessing a significant antiplatelet effect when dosed regularly. As with other NSAIDs, naproxen produces effects that impact the CV system such as renal regulation of fluid balance and regulation of BP.
- Naproxen is associated with a higher risk of GI bleeding than COX-2 inhibitors and other non-selective NSAIDs.

Pharmacology

Naproxen is an NSAID with analgesic, anti-inflammatory, and antipyretic properties. The sodium salt of naproxen is more rapidly absorbed. The mechanism of action of naproxen, like that of other NSAIDs, is not completely understood but may be related to inhibition of COX-1 and COX-2. Naproxen and naproxen sodium are rapidly and completely absorbed after oral administration. It is highly protein-bound and extensively metabolized in the liver (involving UGT2B7, CYP1A2, and CYP2C9); the inactive metabolites are excreted renally.

References

1. Derry S, Wiffen PJ, Moore RA, *et al*. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. *Cochrane Database Syst Rev*. 2017;**7**:CD012638.
2. Magee DJ, Jhanji S, Poulogiannis G, Farquhar-Smith P, Brown MRD. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: a systematic review and reappraisal of the evidence. *Br J Anaesth*. 2019;**123**(2):e412–23.

Nefopam

Generic (POM)
Tablet: 30mg (90).

Indications

- Moderate pain.

Contraindications and cautions

- Contraindicated for use in patients with epilepsy or those receiving a MAOI (see ➔ *Drug interactions*).
- Use with caution in patients with hepatic or renal impairment (see ➔ *Dose adjustments*, p. 494).
- There is a risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when nefopam is used concomitantly with serotonergic drugs. Treatment should be discontinued immediately if this is suspected. Nefopam should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*).
- Nefopam displays anticholinergic and sympathomimetic activity. It should be used with caution in patients with, or at risk of:
  - glaucoma
  - ischaemic heart disease
  - prostatic hypertrophy
  - severe congestive heart failure
  - urinary retention.
- The anticholinergic effect of nefopam can be additive with other drugs. Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Nefopam may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- allergic reactions; angioedema; confusion; convulsions; dizziness; dry mouth; GI disturbances (including abdominal pain and diarrhoea); hallucinations; hypotension; light-headedness; nausea; nervousness; palpitations; paraesthesia; syncope; tremor; urinary retention.

Less frequently:

- anaphylactic reactions; blurred vision; coma; drowsiness; headache; insomnia; sweating; tachycardia; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Currently, there are no recognized pharmacokinetic interactions. The main metabolic pathway appears to be glucuronidation. Co-administration with drugs that affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Pharmacodynamic

- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 493)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *SSRIs*, *tapentadol*, *tramadol*, *trazodone*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticholinergics*—increased risk of adverse effects.
- *Antihypertensives*—increased risk of hypotension.
- *Domperidone*—may inhibit the prokinetic effect.
- *Metoclopramide*—may inhibit the prokinetic effect.
- *SNRIs/SSRIs*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of anticholinergic adverse effects (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).

Dose

Indication

- Initial dose 60mg PO TDS. Dose can be increased to a maximum of 90mg PO TDS.
- Some patients may benefit from a lower dose, e.g. 30mg PO TDS.

Dose adjustments

Elderly

- The SmPC suggests a lower initial dose due to the potential for slower metabolism and the increased risk of CNS adverse effects. Initial dose 30mg PO TDS.

Hepatic/renal impairment

- There are no specific instructions for dose reduction in hepatic impairment. Low initial doses are suggested, and titrate to effect. Given the extensive hepatic metabolism, the SmPC advises caution in hepatic impairment.
- There are no specific instructions for use in renal impairment. The SmPC states that patients with end-stage renal disease might experience increased serum peak concentrations during treatment with nefopam. Lower initial doses are suggested for patients with terminal renal insufficiency.

Additional information

- Tablets will disperse in water with agitation.

Pharmacology

Nefopam is a non-opioid, non-steroidal, centrally acting analgesic drug that exists as a mixture of two enantiomers: (+) S- and (−) R-nefopam. It is chemically distinct to any of the presently known analgesics. It is likely that analgesia involves inhibition of reuptake of dopamine, noradrenaline, and serotonin, with increased neurotransmission in descending pain inhibitory pathways. A proposed mechanism of action involves activation of the 5-HT_7 receptor. Nefopam may also modulate voltage-sensitive Ca^{2+} and Na^{+} channels, thereby affecting glutamic acid pathways and decreased activation of NMDA receptors. It has antimuscarinic, as well as sympathomimetic, activity. Nefopam undergoes extensive metabolism, with <5% of a dose being excreted as unchanged drug. The active metabolite desmethyl-nefopam is produced at very low concentrations. The complete biotransformation of nefopam and its metabolite profile are unknown, although the major route of metabolism is believed to be glucuronidation.

Nifedipine

Standard-release

Generic (POM)
Capsule: 5mg (90); 10mg (90).

Modified-release

Different versions of modified-release preparations may not have the same clinical effect; prescribers should specify the brand to be dispensed.

Branded generic (POM)
Tablet: 10mg (56); 20mg (56); 30mg (28); 40mg (30); 60mg (28).
Capsule: 10mg (60); 20mg (60); 60mg (28).
A variety of other products are available and include Adipine® MR, Adipine® XL, Coracten SR®, Coracten XL®, Fortipine LA®, Nifedipress® MR, Tensipine MR®, and Valni XL®; consult the BNF for more information.

Indications

- Prophylaxis of chronic stable angina (*not discussed*).
- Hypertension (*not discussed*).
- Raynaud's phenomenon (*not discussed*).
- †Smooth muscle spasm pain (e.g. tenesmus).[1]
- †Intractable hiccup.[2]

Contraindications and cautions

- Contraindicated for use in:
  - acute angina
  - clinically significant aortic stenosis
  - during or within 4 weeks of a myocardial infarction
  - unstable angina.
- Standard-release formulations cause a dose-dependent increase in the risk of CV complications (e.g. myocardial infarction); only use if no other treatment suitable.
- Once-daily modified-release formulations are contraindicated for use in inflammatory bowel disease, Crohn's disease, or any degree of GI obstruction.
- Use with caution in patients with:
  - concurrent administration of CYP3A4 inducers or inhibitors (see *Drug interactions*, p. 497)
  - concurrent administration of other antihypertensive drugs (see *Drug interactions*, p. 497)
  - diabetes (can impair glucose tolerance)
  - hepatic impairment
  - low systolic BP (<90mmHg).

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: constipation; headache; oedema; vasodilation.
- *Uncommon*: abdominal pain; allergic reaction (angioedema); anxiety; dizziness; dry mouth; dyspepsia; dysuria; epistaxis; erythema; flatulence;

hypotension; transient elevation in LFTs; migraine; muscle cramps; nasal congestion; nausea; palpitations; polyuria; sexual dysfunction (erectile dysfunction); syncope; tachycardia; tremor; vertigo; visual disturbances.
- *Rare*: gingival hyperplasia; pruritus; rash; urticaria.
- *Unknown*: agranulocytosis; drowsiness; dyspnoea; eye pain; hyperglycaemia; jaundice; leucopenia; photosensitivity; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Nifedipine is metabolized mainly by CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Clarithromycin*—increased effect of nifedipine.
- *Erythromycin*—increased effect of nifedipine.
- *Rifampicin*—significant reduction in the effect of nifedipine.
- Avoid grapefruit juice, as it may increase the bioavailability of nifedipine through inhibition of intestinal CYP3A4.

Pharmacodynamic
- *Alcohol*—potentiates the hypotensive effect of nifedipine.
- The risk of hypotension is increased if nifedipine is taken concurrently with the following drugs:
  - β-blockers; diuretics; haloperidol; levomepromazine; opioids; phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, vardenafil); TCAs.

Dose

+Smooth muscle spasm pain/+intractable hiccup (third- or fourth-line option)

Standard-release
- Initial dose 5mg PO TDS with food (or 30 minutes before food in oesophageal spasm); increase dose as necessary to a maximum of 20mg PO TDS.

Modified-release
- Initial dose 20mg PO OD, or 10mg PO BD; increase dose as necessary to a maximum of 60mg PO daily.

Dose adjustments

Elderly
- No specific guidance is available; use the lowest effective dose.

Hepatic/renal impairment
- No specific guidance is available for patients with hepatic impairment. The SmPC advises caution, given the hepatic metabolism. Use the lowest effective dose.

- Patients with renal impairment are unlikely to need dose adjustments.

Pharmacology

Nifedipine is a dihydropyridine Ca^{2+} channel antagonist. It inhibits the entry of Ca^{2+} through cell membranes by blocking channels. The decrease in intracellular Ca^{2+} inhibits the contractile processes of smooth muscle cells, thereby attenuating spasm.

References

1. McLoughlin R, McQuillan R. Using nifedipine to treat tenesmus. *Palliat Med*. 1997;**11**(5):419–20.
2. Quigley C. Nifedipine for hiccups. *J Pain Symptom Manage*. 1997;**13**(6):313.

Nizatidine

Generic (POM)
Capsule: 150mg (30); 300mg (30).

Indications

- Benign gastric ulcer.
- Duodenal ulcer.
- Gastric and/or duodenal ulcer associated with concomitant use of NSAIDs.
- Gastro-oesophageal reflux disease (including erosions, ulcerations, and associated heartburn).
- Prevention of duodenal or benign gastric ulcer recurrence.

Contraindications and cautions

- Use with caution in patients with hepatic or renal impairment (see *Dose adjustments*, p. 500).

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- elevation of LFTs (mild, transient); somnolence; sweating; urticaria.

Less frequently:

- arthralgia; exfoliative dermatitis; fever; gynaecomastia; hepatitis; hypersensitivity reactions (e.g. anaphylaxis, bronchospasm, eosinophilia, laryngeal oedema, pruritus, rash); hyperuricaemia; impotence; jaundice; myalgia; nausea; reversible mental confusion; serum sickness; thrombocytopenia; thrombocytopenic purpura; vasculitis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Nizatidine is principally excreted via the kidneys, with about 60% as unchanged drug. It is unlikely to be involved in cytochrome-related interactions.
- Drugs with pH-dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced
  - *ferrous sulfate*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g. 100mg) at the same time as ferrous sulfate to improve absorption
  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations
  - *metronidazole suspension*—ranitidine may reduce/prevent the absorption of metronidazole.

Pharmacodynamic
- No clinically significant interactions noted.

Dose

Benign gastric, duodenal, or NSAID-associated ulceration
- 300mg PO OD (evening) for 4–8 weeks; alternatively, 150mg PO BD for 4–8 weeks.
- Maintenance dose of 150mg PO ON.

Treatment of gastro-oesophageal reflux disease
- 150mg to 300mg BD for up to 12 weeks.

Dose adjustments

Elderly
- Usual adult doses can be used.

Hepatic/renal impairment
- Nizatidine is principally excreted via the kidneys, so hepatic impairment is unlikely to have a significant impact. Nonetheless, the SmPC advises caution in hepatic impairment, although there are no specific instructions for dose reduction.
- Nizatidine is principally excreted in the urine. See Table 3.15 for dose adjustments for patients with renal impairment recommended by the SmPC.

Table 3.15 Dose adjustments of nizatidine according to renal impairment

Dose		
Indication	CrCl 20–50mL/min	CrCl <20mL/min
Benign gastric, duodenal, or NSAID-associated ulceration		
Treatment	150mg PO OD (evening)	150mg PO ALT DIE (evening)
Maintenance	150mg PO ALT DIE (evening)	150mg PO every third day (evening)
Gastro-oesophageal reflux disease	150mg PO OD (evening) to 150mg PO BD	150mg PO ALT DIE (evening) to 150mg PO OD (evening)

Pharmacology

Nizatidine is a potent, selective, competitive, and fully reversible H_2 receptor antagonist. It significantly decreases basal and stimulated gastric acid and pepsin concentrations, in addition to the volume of gastric secretions. Nocturnal gastric acid secretion is significantly inhibited for up to 12 hours. Nizatidine has an absolute oral bioavailability of >70%. Approximately 60% of a dose is excreted as unchanged drug, with 90% of the dose being renally eliminated. Moderate to severe renal impairment significantly reduces clearance and prolongs the half-life of nizatidine.

Nortriptyline ♀

Generic (POM)
Tablet: 10mg (28; 30; 84; 100); 25mg (28; 30; 84; 100); 50mg (30).
Oral solution: 10mg/5mL.

Indications

- Depression.
- †Neuropathic pain.[1]

Contraindications and cautions

- Nortriptyline is contraindicated for use in the following:
  - arrhythmias
  - heart block
  - recent myocardial infarction.
- Do not use with an irreversible MAOI (including *rasagiline* and *selegiline*), or within 14 days of stopping one, or at least 24 hours after discontinuation of a reversible MAOI (e.g. *moclobemide*, *linezolid*). Note that in exceptional circumstances, *linezolid* may be given with nortriptyline, but the patient must be closely monitored for symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- There is a *possible* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 502)
  - avoid concomitant administration of drugs that impair elimination (see ➔ *Drug interactions*, p. 502)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- There is a risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when nortriptyline is used concomitantly with serotonergic drugs. Treatment should be discontinued immediately if this is suspected. Nortriptyline should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 502).
- Use with caution in epilepsy (may lower the seizure threshold). *SSRIs* are considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.
- In addition, nortriptyline should be used with caution in patients with:
  - CV disorders
  - diabetes (may alter glycaemic control)
  - hepatic impairment
  - hyperthyroidism or those receiving thyroid medication (enhances response to antidepressant)
  - narrow-angle glaucoma
  - prostatic hypertrophy
  - urinary retention.

- Elderly patients are more susceptible to adverse effects, especially agitation, confusion, and postural hypotension (see ➔ *Dose adjustments*, p. 504). Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- There is an increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs. The mechanism is unknown.
- Nortriptyline may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Avoid abrupt withdrawal as symptoms such as insomnia, irritability, and excessive perspiration can occur. Although generally mild, they can be severe in some patients. Withdrawal symptoms usually occur within the first few days of discontinuing treatment and they usually resolve within 2 weeks, though they can persist in some patients for up to 3 months or longer. See ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants. If withdrawal symptoms emerge during discontinuation, raise the dose to stop symptoms and then restart withdrawal much more gradually.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: accommodation disorder; aggression; congested nose; constipation; dizziness; drowsiness; dry mouth; headache; hyperhidrosis; nausea; palpitations; tachycardia; tremor; weight increase.
- *Common*: agitation; ataxia; atrioventricular block; confusional state; dysgeusia; erectile dysfunction; fatigue; hyponatraemia; decreased libido; micturition disorders; mydriasis; paraesthesia; postural hypotension; QT prolongation; thirst.
- *Uncommon*: anxiety; convulsion; diarrhoea; facial oedema; galactorrhoea; hepatic impairment (e.g. cholestatic liver disease); hypertension; hypomania; insomnia; mania; nightmare; raised intraocular pressure; rash; tinnitus; tongue oedema; urinary retention; urticaria; vomiting.
- *Rare*: abnormal LFTs; alopecia; arrhythmia; blood dyscrasias (e.g. agranulocytosis, leucopenia); reduced appetite; delirium; gynaecomastia; hallucinations; jaundice; paralytic ileus.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Nortriptyline is a substrate of CYP2D6 (major), CYP1A2, and CYP2C19. In patients lacking CYP2D6, the pathways involving CYP1A2 and CYP2C19 become of greater significance. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- If a strong CYP2D6 inhibitor (e.g. fluoxetine, paroxetine, quinidine) or a strong CYP2C19 inhibitor (e.g. fluconazole, omeprazole) is added to nortriptyline treatment, a lower dose of nortriptyline should be considered. There is a risk of prolongation of the QT interval (see ➔ *Contraindications and cautions*, p. 501).

Pharmacodynamic

- Nortriptyline is associated with a possible risk of prolongation of the QT interval. There is a potential risk that co-administration with other drugs that prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 501).
- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 501)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *SSRIs*, *tapentadol*, *tramadol*, *trazodone*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticholinergics*—increased risk of adverse effects.
- *Antidiabetics*—impaired glycaemic control.
- *Anti-epileptics*—nortriptyline antagonizes the effect.
- *Antihypertensives*—possible increased risk of hypotension.
- *CNS depressants*—additive sedative effect.
- *Domperidone*—may inhibit the prokinetic effect.
- *Metoclopramide*—may inhibit the prokinetic effect.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of anticholinergic adverse effects and seizures (and serotonin toxicity).
- *SNRIs/SSRIs*—increased risk of seizures (and serotonin toxicity).
- *Sympathomimetics*—(e.g. *adrenaline*, *phenylpropanolamine*, *salbutamol*) combination may predispose patients to cardiac arrhythmias and hypertension.
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

Depression

- 10mg to 25mg PO ON, increasing as necessary to a usual dose of 75mg to 100mg daily in 3–4 divided doses, or as a single dose (e.g. at bedtime).

†Neuropathic pain

- 10mg to 25mg PO ON, increasing as necessary to a maximum of 50mg PO daily in divided doses, or as a single dose (e.g. at bedtime). Higher doses may be used under specialist supervision.

The SmPC advises monitoring of nortriptyline plasma concentrations if a dose above 100mg daily is prescribed (optimum range of 50ng/mL to150ng/mL), although the practical value is uncertain.

Consider a dose reduction of 50% for patients who are known or suspected to be CYP2C19 and CYP2D6 poor metabolizers, due to the increased risk of dose-dependent adverse effects.

Dose adjustments

Elderly

- Elderly patients are particularly susceptible to adverse anticholinergic effects, with an increased risk of cognitive decline and dementia. No specific dose reductions are recommended by manufacturers. However, it is suggested that elderly patients are initiated on the lower end of the usual range, i.e. for pain, 10mg PO ON, and the dose increased as necessary and as tolerated.

Hepatic/renal impairment

- There are no specific instructions for dose reduction in hepatic impairment. The SmPC advises caution if nortriptyline is to be used in patients with advanced liver disease. If the drug has to be used, the patient should be closely monitored and the lowest effective dose should be prescribed. The SmPC suggests the use of plasma monitoring.
- The SmPC states no dose adjustments are required in patients with renal impairment.

Additional information

- Nortriptyline may have a better adverse effect profile than amitriptyline, specifically less anticholinergic effects.
- May have immediate benefits in treating insomnia or anxiety; antidepressant action may be delayed by 2–4 weeks.

Pharmacology

Nortriptyline is the primary active metabolite of amitriptyline. It has a similar mechanism of action and receptor profile to amitriptyline, although it has a stronger affinity for NET than for SERT, and a lesser action at muscarinic receptors. The interference with the reuptake of noradrenaline and serotonin is believed to explain the mechanism of the antidepressant and the analgesic activity of nortriptyline.

Nortriptyline undergoes hepatic metabolism by a variety of cytochromes (CYP1A2, CYP2C19 [major], and CYP2D6 [major]) to several weakly active metabolites. Further metabolism involves glucuronidation, followed by

excretion via the urine. Only small amounts are excreted via bile, or as unchanged drug in the urine.

Reference

1. van den Beuken-van Everdingen MH, de Graeff A, Jongen JL, *et al*. Pharmacological treatment of pain in cancer patients: the role of adjuvant analgesics, a systematic review. *Pain Pract*. 2017;**17**(3):409–19.

Nystatin

Generic (POM)
Oral suspension: 100,000 units/mL (30mL).

Indications

- Candidal infections of the oral cavity and oesophagus.

Contraindications and cautions

- None stated.

Adverse effects

Frequency is not stated, but reported adverse effects include:

- diarrhoea (more likely with high doses); hypersensitivity; nausea; oral irritation; vomiting.

Drug interactions

Pharmacokinetic

- None known.

Pharmacodynamic

- *Chlorhexidine*—nystatin inactivated by chlorhexidine; separate administration by at least 1 hour.

Dose

- Initial dose 4mL to 6mL PO QDS[+], rinsed around the mouth for 1 minute before swallowing, for a usual duration of 7 days.
- Licensed dose is 1mL PO QDS, but this will not provide sufficient contact with the lesions.
- Patients with dentures should remove them before using nystatin and clean them before reinsertion. Overnight, dentures should be soaked in an appropriate antiseptic solution (and rinsed before reinsertion).

Dose adjustments

Elderly

- Dose adjustments are unnecessary.

Hepatic/renal impairment

- Dose adjustments are unnecessary.

Pharmacology

Nystatin is a polyene anti-fungal drug active against a wide range of yeasts and yeast-like fungi, including *Candida albicans*. Nystatin acts by binding to the cell membrane, causing a change in membrane permeability and subsequent leakage of intracellular components. *C. albicans* (the organism responsible for the majority of oral candidosis) does not develop resistance to nystatin. Other species of *Candida* can become quite resistant during treatment, resulting in cross-resistance to amphotericin. This resistance is lost once nystatin is discontinued.

Absorption of nystatin from the GI tract is negligible; excessive doses tend only to produce GI adverse effects such as diarrhoea, nausea, and vomiting.

Octreotide ⚠

Sandostatin® (POM)

Injection: 50 micrograms/mL (5); 100 micrograms/mL (5); 1mg/5mL (multi-dose vial); 500 micrograms/mL (5).

Generic (POM)

Injection: 50 micrograms/mL (5); 100 micrograms/mL (5); 1mg/5mL (multi-dose vial); 500 micrograms/mL (5).

Prefilled syringes: 50 micrograms/mL (5); 100 micrograms/mL (5); 500 micrograms/mL (5).

Prolonged-release suspension for injection

Sandostatin® LAR (POM)

Injection: 10mg (1); 20mg (1); 30mg (1).

Generic (POM)

Injection: 10mg (1); 20mg (1); 30mg (1).

Use of prolonged-release suspension for injection may be subject to local health economy guidelines. Its use is not discussed here.

Indications

- Acromegaly (*not discussed*).
- Prevention of complications following pancreatic surgery (*not discussed*).
- Emergency treatment of bleeding gastro-oesophageal varices in patients with cirrhosis (*not discussed*).
- Relief of symptoms associated with functional gastroenteropancreatic (GEP) endocrine tumours (e.g. carcinoid, VIPomas, glucagonomas).
- Anti-secretory effect:
  - †large-volume vomiting associated with bowel obstruction[1]
  - †excessive diarrhoea[2]
  - †bronchorrhoea[3]
  - †ascites[4]
  - †tumour-related secretions.[5]

Contraindications and cautions

- Abrupt withdrawal of SUBCUT octreotide is associated with biliary colic and pancreatitis.
- Octreotide reduces gall bladder motility and there is a risk of gallstone development.
- Use with caution in patients with:
  - Type 1 diabetes (insulin doses may need reducing)
  - Type 2 diabetes (dose adjustment may be needed)
  - hepatic impairment (the half-life of octreotide may be increased—dose reduction may be necessary).
- The SmPC states that hepatic and thyroid function should be monitored during treatment with octreotide.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: abdominal pain; cholelithiasis; constipation; diarrhoea; flatulence; headache; hyperglycaemia; local injection site pain, swelling and irritation; nausea.
- *Common*: abdominal bloating; alopecia; anorexia; asthenia; bradycardia; cholecystitis; discoloration of faeces; dizziness; dyspepsia; dyspnoea; elevated LFTs; hyperbilirubinaemia; hypoglycaemia; hypothyroidism; impaired glucose tolerance; loose stools; pruritus; rash; steatorrhoea; thyroid disorder (e.g. decreased TSH, decreased total thyroxine (T4), and decreased free T4); vomiting.
- *Uncommon*: dehydration; tachycardia.
- *Not known*: acute hepatitis; acute pancreatitis (reported to occur within the first hours or days); arrhythmias; cholestasis; cholestatic hepatitis; hypersensitivity; jaundice; thrombocytopenia; urticaria.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Through suppression of growth hormone, octreotide may reduce the metabolic clearance of drugs metabolized by the cytochrome P450 system. The prescriber should be aware that drugs mainly metabolized by CYP3A4 and with a narrow therapeutic index may need dose adjustments.
- Octreotide can reduce the absorption of *ciclosporin*, potentially resulting in reduced plasma levels and possible treatment failure.

Pharmacodynamic

- *Anticholinergics*—additive anti-secretory effect.
- *Antidiabetic drugs*—dose adjustments may be necessary due to the effect on glucose regulation.
- *Antihypertensives*—dose adjustments may be required due to the risk of bradycardia.
- *Insulin*—dose adjustments may be necessary due to the effect on glucose regulation.

Dose

GEP tumours

- Initial dose 50 micrograms SUBCUT OD to BD. Increase according to response to a maximum of 200 micrograms TDS. To reduce pain on administration, ensure the ampoule is warmed to room temperature beforehand.
- [+]Alternatively, 100 micrograms daily via CSCI. Increase as necessary to 600 micrograms daily.
- Discontinue after 1 week if no improvement.

[+]Anti-secretory effect

- Initial dose 200micrograms to 500 micrograms daily via CSCI. Dose can be increased to a usual maximum of 600 micrograms daily. Higher doses (e.g. 1500 micrograms) have been used successfully.

- Alternatively, 50micrograms to 100 micrograms SUBCUT TDS, increased as necessary to 200 micrograms SUBCUT TDS. To reduce pain on administration, ensure the ampoule is warmed to room temperature beforehand.

Dose adjustments

Elderly

- Normal doses can be used.

Hepatic/renal impairment

- The manufacturer advises that a dose reduction may be necessary in patients with hepatic impairment.
- No dose adjustments are necessary for patients with renal impairment.

Additional information

- Octreotide is reportedly *chemically and physically* compatible under stated conditions with diamorphine.[6]
- Under stated conditions, octreotide is reportedly *physically* compatible with alfentanil, clonazepam, cyclizine, diamorphine, glycopyrronium, haloperidol, hydromorphone, hyoscine butylbromide, hyoscine hydrobromide, levomepromazine, metoclopramide, midazolam, morphine sulfate, ondansetron, oxycodone, and ranitidine.[6]
- Combination with an anticholinergic drug, such as glycopyrronium, may have an additive anti-secretory effect.

Pharmacology

Octreotide is a synthetic analogue of the inhibitory hormone somatostatin (SST). The effects of octreotide are mediated via SST receptors, which are found in a wide variety of normal tissues. There are five distinct SST receptors ($SSTR_{1-5}$), to which SST binds with a high affinity to elicit its actions. Octreotide, however, binds with relative selectivity to $SSTR_2$, $SSTR_3$, and $SSTR_5$. Interestingly, $SSTR_2$, $SSTR_3$, and $SSTR_5$ are expressed by malignant lymphomas, as well as certain endocrine tumours.

Following SUBCUT injection, octreotide is rapidly absorbed, with a bioavailability approaching 100%. Approximately 30–40% of a dose undergoes hepatic metabolism, with up to 32% of a dose being excreted in the urine unchanged.

References

1. Davis M, Hui D, Davies A, *et al*. Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. *Support Care Cancer*. 2021;**29**(12):8089–96.
2. Bossi P, Antonuzzo A, Cherny NI, *et al*. Diarrhoea in adult cancer patients: ESMO clinical practice guidelines. *Ann Oncol*. 2018;**29**(Suppl 4):126–42.
3. Rémi C, Rémi J, Bausewein C. Pharmacological management of bronchorrhea in malignant disease: a systematic literature review. *J Pain Symptom Manage*. 2016;**51**(5):916–25.
4. Kalambokis G, Fotopoulos A, Economou M, Tsianos EV. Octreotide in the treatment of refractory ascites of cirrhosis. *Scand J Gastroenterol*. 2006;**41**(1):118–21.
5. Harvey M, Dunlop R. Octreotide and the secretory effects of advanced cancer. *Palliat Med*. 1996;**10**(4):346–7.
6. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Olanzapine ⚠ ♡

Zyprexa® (POM)
Tablet: 2.5mg (28); 5mg (28); 7.5mg (56); 10mg (28); 15mg (28); 20mg (28).

Zyprexa Velotab® (POM)
Orodispersible tablet: 5mg (28); 10mg (28); 15mg (28); 20mg (28).

Generic (POM)
Tablet: 2.5mg (28); 5mg (28); 7.5mg (56); 10mg (28); 15mg (28); 20mg (28).
Orodispersible tablet: 5mg (28); 10mg (28); 15mg (28); 20mg (28).

Unlicensed (POM)
Injection: 10mg powder (see *Additional information*, p. 514).

Indications

- Psychosis.
- Treatment-resistant depression.[1]
- †Nausea and vomiting.[2]
- †Delirium.[3]
- †Terminal agitation refractory to conventional treatment.[2]

Contraindications and cautions

⚠ Warning
- Antipsychotic drugs have been associated with an elevated risk of VTE. Several potential mechanisms have been described, including drug-induced sedation, obesity, hyperprolactinaemia, increased platelet aggregation (by 5-HT_2 antagonism), and elevation of antiphospholipid antibody.
- Olanzapine should not be used to treat behavioural symptoms of dementia. Elderly patients with dementia-related psychosis treated with olanzapine are at increased risk of CVA and mortality.
- A risk of excess mortality has been consistently observed in elderly patients with dementia treated with antipsychotics. The mechanism of mortality may be CV in nature (e.g. arrhythmia susceptibility from QT prolongation or increased risk of VTE). Conventional antipsychotics (e.g. haloperidol) are likely to carry a greater risk of mortality than atypical antipsychotics (e.g. quetiapine, risperidone).
- The risks associated with CVA (e.g. diabetes, hypertension, smoking) should be assessed before commencing treatment with olanzapine.

- Must not be used in patients with a known risk of narrow-angle glaucoma.
- Use with caution in:
  - diabetes (risk of hyperglycaemia in the elderly; increased risk of CVA)
  - epilepsy (seizure threshold may be lowered)
  - hepatic/renal impairment (see *Dose adjustments*, p. 514)
  - Parkinson's disease (olanzapine shows no efficacy for psychosis and may aggravate motor symptoms)

  - phenylketonuria (orodispersible tablet contains aspartame, a source of phenylalanine).
- There is a *conditional* risk of QT prolongation/TdP. Although considered low risk,[4] the SmPC recommends to:
  - avoid concomitant administration of drugs that prolong the QT interval (see *Drug interactions*, p. 512)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment.
- Appropriate monitoring of weight, blood glucose, and lipids is advisable if treatment persists beyond 3 months to detect antipsychotic-induced changes. In addition, an increase in body weight may be a predisposing factor for the development or exacerbation of diabetes.
- Concurrent use of adrenaline and antipsychotics may cause dose-dependent severe hypotension and tachycardia (α-adrenergic antagonist effects of antipsychotics can result in decreased peripheral resistance, and adrenaline may have significant β_2-adrenergic-mediated vasodilatory effects).
- Avoid sudden discontinuation, as this may lead to the development of acute withdrawal symptoms (e.g. sweating, insomnia, tremor, anxiety, nausea and vomiting, Parkinson's-like symptoms).
- Sudden cessation of tobacco smoking may lead to the development of adverse effects associated with excess dose (loss of CYP1A2 induction).
- If a patient develops signs and symptoms indicative of NMS, such as altered mental status, autonomic instability (e.g. cardiac dysrhythmia, diaphoresis), hyperpyrexia, and muscle rigidity, or presents with unexplained high fever without additional clinical manifestations of NMS, olanzapine must be discontinued.
- Elderly patients are more susceptible to adverse effects (see *Dose adjustments*, p. 514). Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Therapeutic doses of olanzapine can precipitate an acute confusional state in vulnerable individuals. This may be related to the anticholinergic effects of olanzapine.
- Olanzapine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: drowsiness; postural hypotension; elevated prolactin levels; weight gain (≥7% of baseline body weight with short-term treatment; with long-term exposure, defined as >48 weeks, weight gain may be ≥25% of baseline body weight).
- *Common*: akathisia; increased appetite; arthralgia; asthenia; constipation; dizziness; dry mouth; fatigue; glucosuria; hypercholesterolaemia; hyperglycaemia; hypertriglyceridaemia; injection site discomfort; raised

LFTs; neutropenia; oedema; sexual dysfunction (erectile dysfunction, reduced libido); weight gain (≥15% of baseline body weight with short-term treatment).
- *Uncommon*: alopecia; amnesia; bradycardia; diabetes (development or exacerbation); photosensitivity; QT prolongation; restless legs syndrome; seizures (in patients with a history of or risk factors for); sexual dysfunction (amenorrhoea, breast enlargement, galactorrhoea, gynaecomastia); thromboembolism.
- *Unknown*: diabetes (development of exacerbation); DRESS (drug rash with eosinophilia and systemic symptoms); hepatitis; hypothermia; NMS (see ➔ *Contraindications and cautions*, p. 510); pancreatitis; seizures; thrombocytopenia; withdrawal symptoms upon sudden discontinuation.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Is metabolized mainly by glucuronidation via UGT1A4 and UGT2B10, but CYP1A2 is involved to a lesser degree. CYP2D6 has a minor role.
- Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, CYP1A2 may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index. Co-administration of CYP2D6 inhibitors is unlikely to be of any clinical significance.
- Tobacco smoking may lead to faster metabolism of olanzapine. Dose adjustments may be necessary upon smoking cessation (see Box 1.11).

Pharmacodynamic
- Olanzapine can cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone, quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 510).
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Adrenaline*—α-adrenergic effects may be blocked, with consequential paradoxical hypotension and tachycardia.
- *Anticholinergics*—increased risk of adverse effects.
- *Antidiabetics*—impaired glycaemic control (risk of hyperglycaemia).
- *Antihypertensives*—increased risk of hypotension.
- *CNS depressants*—additive sedative effect.
- *Domperidone*—may reduce the prokinetic effect.
- *Haloperidol*—increased risk of extrapyramidal reactions.
- *Levodopa and dopamine agonists*—effect antagonized by olanzapine.
- *Levomepromazine*—increased risk of extrapyramidal reactions.
- *Metoclopramide*—increased risk of extrapyramidal reactions; reduced prokinetic effect.

- *Nefopam*—increased risk of anticholinergic adverse effects.
- *Opioids*—may be an additive hypotensive effect.
- *Trazodone*—may be an additive hypotensive effect (and prolongation of the QT interval).

Dose

Psychosis

- Initial dose 10mg PO OD, adjusted on the basis of individual clinical response within the range of 5mg/day to 20mg/day.

+Depression

- To be used under the guidance of a specialist for the management of treatment-resistant depression. Used in combination with an SSRI or SNRI.
- Initial dose 5mg PO ON, increased as necessary to a maximum of 20mg PO ON.

- Anecdotal, unpublished reports describe successful unlicensed administration of olanzapine by CSCI. Note, however, that the manufacturer recommends the reconstituted injection solution is used within 1 hour. The prescriber must consider this before initiating a CSCI. See *Additional information*, p. 514 for reconstitution details.
- Similarly, the IM preparation has been administered by SUBCUT injection and is reportedly well tolerated.
- Note that oral bioavailability of olanzapine approaches 60%.[5] When converting a patient from PO to SUBCUT/CSCI, a dose reduction of between 25% and 50% should be considered.

+Nausea and vomiting

- Initial dose 2.5mg PO ON, increased as necessary to a maximum of 10mg PO ON.
- Alternatively, initial dose 2.5mg SUBCUT ON or via CSCI, increased as necessary to a maximum of 10mg/day.

+Delirium

- Initial dose 2.5mg PO ON, increased as necessary to a maximum of 20mg PO ON.
- Alternatively, initial dose 2.5mg to 5mg SUBCUT every 8 hours. One report suggests this can be increased to 10mg SUBCUT every 8 hours if necessary.[2] Another option is 2.5mg to 5mg via CSCI, increased as necessary to a usual maximum dose of 20mg/day, although this may be increased to 30mg/day.[2]

+Terminal agitation

- Initial dose 2.5mg to 5mg SUBCUT every 8 hours. One report suggests this can be increased to 10mg SUBCUT every 8 hours if necessary.[2]
- Alternatively, 2.5mg to 5mg via CSCI, increased as necessary to a usual maximum dose of 20mg/day, although this may be increased to 30mg/day.[2]

Dose adjustments

Elderly

- Note that the elderly are more susceptible to the anticholinergic adverse effects, which may increase the risk of cognitive decline and dementia.
- For psychosis, initial dose 5mg PO daily.
- For depression, initial dose 2.5mg PO daily.
- For delirium, nausea, and vomiting, increase the dose gradually to improve tolerance.
- For terminal agitation, initial dose 2.5mg SUBCUT or via CSCI.

Hepatic/renal impairment

- For psychosis, initial dose 5mg daily (in both cases).
- For delirium, nausea, and vomiting, increase the dose gradually to improve tolerance.
- For terminal agitation, initial dose 2.5mg SUBCUT or via CSCI.

Additional information

- The orodispersible tablet may be placed on the tongue and allowed to dissolve or dispersed in water, orange juice, apple juice, milk, or coffee.
- Patients can gain an average of 3 kg within 6 weeks, and 10 kg at 38 weeks, with olanzapine treatment.[6]
- Risk factors for a poor response to olanzapine in cancer patients with delirium include:
  - age >70 years
  - history of dementia
  - CNS metastases.
- Olanzapine injection should be reconstituted as follows:
  - withdraw 2.1mL of WFI into a sterile syringe. Inject into the vial and completely dissolve the contents
  - the vial contains olanzapine 5mg/mL
  - for a 10mg dose, withdraw 2mL as there may be an overage in the vial (i.e. do not use the entire content of the reconstituted vial).
- Compatibility information for olanzapine injection is presently limited and it is recommended to be given via a separate CSCI. NaCl or WFI can be used as a diluent once it has been reconstituted.

Pharmacology

Olanzapine is a second-generation antipsychotic agent, which interacts with a wide range of receptors in producing its antipsychotic therapeutic effects, including 5-$HT_{2A/2C}$ (inverse agonism) and D_1–D_4 (antagonism). There is a greater affinity for 5-$HT_{2A/2C}$ receptors than for D_2 receptors, which explains the lower incidence of extrapyramidal adverse effects, compared to first-generation antipsychotics. It also antagonizes additional receptors, which explains the range of effects that are produced; these include 5-HT_3, 5-HT_6, muscarinic M_1–M_5, α_1-adrenergic, and H_1 receptors. Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5–8 hours. It is mainly metabolized in the liver by glucuronidation, although some oxidation via CYP1A2 does occur. CYP2D6

also has a minor role in the metabolism of olanzapine. The main metabolite of olanzapine is inactive.

References

1. Ruberto VL, Jha MK, Murrough JW. Pharmacological treatments for patients with treatment-resistant depression. *Pharmaceuticals (Basel)*. 2020;**13**(6):116.
2. Walsh D, Davis M, Ripamonti C, Bruera E, Davies A, Molassiotis A. 2016 Updated MASCC/ESMO consensus recommendations: management of nausea and vomiting in advanced cancer. *Support Care Cancer*. 2017;**25**(1):333–40.
3. Elsayem A, Bush SH, Munsell MF, *et al*. Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study. *J Pain Symptom Manage*. 2010;**40**(5):774–82.
4. Lambiase PD, de Bono JP, Schilling RJ, *et al*. British Heart Rhythm Society clinical practice guidelines on the management of patients developing QT prolongation on antipsychotic medication. *Arrhythm Electrophysiol Rev*. 2019;**8**(3):161–5.
5. Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine. Pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet*. 1999;**37**(3):177–93.
6. Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLoS One*. 2014;**9**(4):e94112.

Omeprazole ♡

Losec® (POM)
Capsule: 10mg (28); 20mg (28); 40mg (7).

Losec® MUPS® (POM)
Tablet: 10mg (28); 20mg (28); 40mg (7).

Generic (POM)
Capsule 10mg (28); 20mg (28); 40mg (7; 28).
Tablet: 10mg (28); 20mg (28); 40mg (7).
Dispersible tablet: 10mg (28); 20mg (28); 40mg (7).
Oral suspension: 10mg/5mL (75mL; 90mL); 20mg/5mL (75mL; 90mL).
IV infusion: 40mg (5).
NB—omeprazole 10mg tablets can be sold OTC for short-term relief of reflux-like symptoms (e.g. heartburn) in adults over 18 years; maximum daily dose of 20mg PO for a maximum of 4 weeks, and a pack size of 28 tablets.

Indications

- Treatment of gastric and duodenal ulcers.
- Treatment of reflux oesophagitis.
- Treatment and prophylaxis of NSAID-associated benign gastric and duodenal ulcers requiring continual therapy.
- Symptomatic gastro-oesophageal reflux disease.
- Eradication of *Helicobacter pylori* (*not discussed*).
- Zollinger–Ellison syndrome (*not discussed*).

Contraindications and cautions

- Increased gastric pH resulting from omeprazole treatment may critically affect the absorption of certain drugs (see ➔ *Drug interactions*, p. 517).
- Treatment with omeprazole may lead to a slightly increased risk of developing GI infections (e.g. *Clostridium difficile*). Therefore, avoid unnecessary use or high doses.
- Rebound acid hypersecretion may occur on discontinuation if the patient has received >8 weeks' treatment.
- Omeprazole is predominantly metabolized by CYP2C19 and by CYP3A4 to a lesser extent. Factors affecting CYP2C19 activity, such as phenotype (see Box 1.3) and drugs (see ➔ *Drug interactions*, p. 517), can alter response and adverse effects.
- PPIs are associated with a range of electrolyte disturbances such as hyponatraemia and hypomagnesaemia (and associated hypocalcaemia and hypokalaemia). Suspect the PPI, should unexplainable symptoms present (e.g. confusion, delirium, generalized weakness, nausea). The effect on Na^+ metabolism is unclear, possibly involving ADH. PPIs may reduce active Mg^{2+} absorption in the small intestine by affecting the function of a transient receptor protein channel. Poor metabolizer status may contribute to such adverse effects.
- There is a *conditional* risk of QT prolongation/TdP due to the propensity to cause significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia). Monitor electrolytes regularly in patients with known QT interval prolongation or congenital long QT

syndrome and in those taking drugs that prolong the QT interval (see ➔ *Drug interactions*).
- When used in high doses and over long durations (>1 year), PPIs may increase the risk of hip, wrist, and spine fracture, predominantly in the elderly or in the presence of other recognized risk factors. Consider the need for adequate vitamin D and calcium intake.
- Omeprazole may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Common*: abdominal pain; constipation; diarrhoea; flatulence; fundic gland polyps (benign); headache; nausea; vomiting.
- *Uncommon*: dermatitis; dizziness; drowsiness; dry mouth; fracture (hip, spine, or wrist); insomnia; increased liver enzymes; malaise; peripheral oedema; pruritus; raised liver enzymes; rash; urticaria; vertigo.
- *Rare*: agitation; alopecia; arthralgia; bronchospasm; confusion; depression; dry mouth; GI candidosis; hepatitis with or without jaundice; hypersensitivity reactions (e.g. fever, angioedema); hyponatraemia; interstitial nephritis; leucopenia; malaise; myalgia; photosensitivity; stomatitis; increased sweating; taste disturbance; thrombocytopenia; visual disturbances (e.g. blurred vision).
- *Very rare*: aggression; agranulocytosis; erythema multiforme; gynaecomastia; hallucinations; hepatic failure; muscular weakness; pancytopenia; renal failure; Stevens–Johnson syndrome; toxic epidermal necrolysis.
- *Not known*: hypomagnesaemia (may correlate with hypocalcaemia and/or hypokalaemia).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Omeprazole is metabolized by CYP2C19 and CYP3A4. It is a strong inhibitor of CYP2C19, with weak inhibitory effects on CYP2C9, CYP2D6, and CYP3A4. Omeprazole is also a substrate and an inhibitor of P-gp. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Drugs with pH-dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced

  - *ferrous sulfate*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g. 100mg) at the same as ferrous sulfate to improve absorption
  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations
  - *metronidazole suspension*—omeprazole may reduce/prevent the absorption of metronidazole.
- *Azole anti-fungals*—fluconazole may cause increased omeprazole concentrations (CYP2C19 inhibition).
- *Citalopram*—omeprazole can increase the plasma concentration of citalopram through inhibition of CYP2C19.
- *Clarithromycin*—inhibition of CYP3A4 metabolism can lead to increased omeprazole concentrations.
- *Clopidogrel*—antiplatelet action may be reduced (the SmPC recommends to avoid combination).
- *Diazepam*—plasma concentrations of diazepam can be increased through inhibition of CYP2C19.
- *Escitalopram*—omeprazole can increase the plasma concentration of escitalopram through inhibition of CYP2C19.
- *Methotrexate*—omeprazole may cause increases in the level of methotrexate; consider withholding omeprazole.
- *Modafinil*—may cause increased omeprazole concentrations (CYP2C19 inhibition).
- *Tacrolimus*—serum levels of tacrolimus may be increased by omeprazole.
- *Phenytoin*—monitoring phenytoin plasma concentration is recommended (refer to the SmPC).
- *Voriconazole*—inhibition of CYP2C19 by omeprazole may increase levels of voriconazole.
- *Warfarin*—possible increase in INR.
- The clinical significance of co-administration with CYP2C19 inducers or inhibitors (see ➔ *Inducers* and *Inhibitors* on the inside back cover) is unknown. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary.
- The clinical significance of co-administration with CYP3A4 inducers or inhibitors (see ➔ *Inducers* and *Inhibitors* on the inside back cover) is unknown. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary.
- The clinical significance of co-administration of other CYP2C19 substrates (see ➔ *Substrates* on the inside back cover) is unknown. Caution is advised if omeprazole is co-administered with drugs that are predominantly metabolized by CYP2C19. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Pharmacodynamic

- Omeprazole may cause prolongation of the QT interval due to the propensity to cause electrolyte disturbances. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*,

domperidone, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.
- *Corticosteroids*—concurrent use may increase the risk of osteoporosis and osteoporotic fractures.

Dose

Duodenal and benign gastric ulcers
- Initial dose 20mg PO OD for 4 weeks in duodenal ulceration or 8 weeks in gastric ulceration.
- In severe or recurrent cases, the dose may be increased to 40mg PO OD.
- Maintenance treatment for recurrent gastric/duodenal ulcers is recommended at a dose of 20mg PO OD.
- Alternatively, in patients unable to tolerate oral therapy, 40mg IV or IVI OD until PO administration possible.

Reflux oesophagitis
- Initial dose 20mg PO OD for 4–12 weeks. For refractory disease, 40mg PO OD has been given for 8 weeks.
- Maintenance 10mg to 20mg PO OD if necessary.
- Alternatively, in patients unable to tolerate oral therapy, 40mg IV or IVI OD until PO administration possible.

Treatment of NSAID-associated peptic ulcer disease
- Initial dose 20mg PO OD, continued for 4–8 weeks.
- Alternatively, in patients unable to tolerate oral therapy, 40mg IV injection or IVI OD until PO administration possible.

Prophylaxis of NSAID-associated peptic ulcer disease
- 20mg PO OD.

Symptomatic gastro-oesophageal reflux disease
- 10mg to 20mg PO OD for 2–4 weeks, depending on the severity and persistence of symptoms.

Dose adjustments

Elderly
- Dose adjustments are not necessary in the elderly.

Hepatic/renal impairment
- In hepatic impairment, the dose should not exceed 20mg PO OD.
- Dose adjustments are not required for patients with renal impairment.

Additional information

- *Losec® MUPS®* tablets (and certain generic formulations) release e/c pellets when dissolved in water. The tablet can be dispersed in 10mL of water prior to administration. Alternatively, fruit juice (e.g. apple, orange) can also be used. The mixture should be stirred before drinking and it is recommended that half a glass of water is taken afterwards. The e/c pellets must not be chewed.
- The content of *Losec®* capsules (or certain generic formulations) can be swallowed directly with half a glass of water or may be suspended

in 10mL of water prior to administration. Alternatively, fruit juice or non-carbonated water can be used. The mixture should be stirred before drinking and it is recommended that half a glass of water is taken afterwards.
- For administration via an 8Fr nasogastric tube, dispersible tablets (refer to the SmPC) or oral suspension should be used.
- Omeprazole IV injection is to be given slowly over a period of 5 minutes.
- Omeprazole IVI should be administered in either 100mL of NaCl or 100mL of GLU over 20–30 minutes.

Pharmacology

Omeprazole is a PPI that suppresses gastric acid secretion in a dose-related manner by specific inhibition of H^+/K^+-ATPase in the gastric parietal cell. Oral bioavailability is moderate (≈ 60% after repeated dosing). It is extensively metabolized, mainly by CYP2C19, although several alternative pathways are involved (e.g. CYP2C8/9, CYP2D6, CYP3A4). Note that CYP2C19 poor metabolizers (or patients taking CYP2C19 inhibitors) can have significantly higher plasma concentrations, leading to unexpected results.

Ondansetron ♥

Zofran® (POM)
Tablet: 4mg (30); 8mg (10).
Syrup (sugar-free): 4mg/5mL (50mL).
Injection: 4mg/2mL (5); 8mg/4mL (5).
Suppository: 16mg (1).

Zofran Melt® (POM)
Oral lyophilisate: 4mg (10); 8mg (10).

Generic (POM)
Tablet: 4mg (10; 30); 8mg (10).
Orodispersible film: 4mg (10); 8mg (10) (*Setofilm®*).
Orodispersible tablet: 4mg (10); 8mg (10).
Oral solution (sugar-free): 4mg/5mL (50mL).
Injection: 4mg/2mL (5); 8mg/4mL (5).

Indications

- Nausea and vomiting (post-operative, chemotherapy, or radiotherapy-induced).
- †Nausea and vomiting (e.g. drug-induced, cancer-related, refractory).[1]
- †Pruritus (e.g. cholestatic, uraemic, opioid-induced).[2]

Contraindications and cautions

- Must not be used with apomorphine (see ➔ *Drug interactions*, p. 522).
- There is a *known* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 522)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - use with caution in patients with significant bradycardia, and in patients with recent acute myocardial infarction or uncompensated heart failure.
- Serotonin syndrome has been reported in patients using ondansetron (see ➔ Chapter 1, *Serotonin toxicity*, p. 29). Treatment should be discontinued immediately if this is suspected. Ondansetron should not be used concomitantly with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 522).
- Since ondansetron increases large bowel transit time, use with caution in patients with signs of subacute bowel obstruction.
- Use with caution in patients with:
  - cardiac rhythm or conduction disturbances (e.g. QT interval prolongation)
  - concurrent use of antiarrhythmic agents or β-adrenergic blocking agents (see ➔ *Drug interactions*, p. 522)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 523)
  - significant electrolyte disturbances.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: headache.
- *Common*: constipation; flushing; local irritation (PR/IV/SUBCUT).
- *Uncommon*: abnormal LFTs; arrhythmias; bradycardia; chest pain; extrapyramidal reactions; hiccups; hypotension; seizures.
- *Rare*: dizziness (after rapid IV injection); hypersensitivity (including anaphylaxis); QT prolongation (including TdP); transient visual disturbances (e.g. blurred vision—mainly IV administration).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized by a variety of cytochromes (e.g. CYP1A2, CYP2D6) but is a major substrate of CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index. Note that co-administration of an enzyme inhibitor is unlikely to be clinically significant due to metabolism via multiple pathways.
- *Carbamazepine*, *phenytoin*, *and rifampicin* can reduce ondansetron levels and reduce the effect.
- The clinical significance of co-administration with other CYP3A4 inducers or inhibitors (see ➔ *Inducers* and *Inhibitors* on the inside back cover) is unknown. The prescriber should be aware of the potential for interactions and that dose adjustments may be necessary.
- The effect of grapefruit juice on the absorption of ondansetron is unknown.

Pharmacodynamic

- Ondansetron has been reported to cause prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 521).
- Risk of serotonin syndrome with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 521)
  - *serotonergic drugs*—e.g. *duloxetine*, *fentanyl*, *methadone*, *mirtazapine*, *tramadol*, *trazodone*, *venlafaxine*.
- Ondansetron increases bowel transit time. This effect can be enhanced by drugs such as *opioids*, *TCAs*, and *anticholinergics*.
- *Apomorphine*—there have been reports of profound hypotension and loss of consciousness (*avoid combination*).
- *Domperidone/metoclopramide*—ondansetron reduces the prokinetic effect.
- *Paracetamol*—possible reduced analgesic benefit.
- *Tramadol*—reduced analgesic benefit; risk of serotonin syndrome.

Dose

+*Nausea and vomiting (e.g. drug-induced, cancer-related, refractory)*

- Initial dose 4mg to 8mg PO/SUBCUT BD to TDS.
- Alternatively, 8mg to 16mg via CSCI daily. The dose can be increased, if necessary, to a maximum of 32mg daily.
- Alternatively, 16mg PR OD.

+*Pruritus*

- Initial dose 4mg PO/SUBCUT BD, increasing if necessary to 8mg PO/SUBCUT TDS. Treatment may be continued via CSCI if necessary.

Dose adjustments

Elderly

- Adult doses can be used.

Hepatic/renal impairment

- In moderate or severe hepatic impairment, the SmPC states that a total daily dose of 8mg should not be exceeded (no dose adjustment necessary for *granisetron*).
- No dose adjustments are necessary for patients with renal impairment.

Additional information

- 5-HT_3 antagonists differ in chemical structure, pharmacokinetics, and pharmacodynamics. There may be individual variation in response, and it may be worth considering an alternative 5-HT_3 antagonist if response to ondansetron is not as expected.
- Treatment with ondansetron should be used regularly for 3 days, and then response assessed. Avoid using on a PRN basis.
- Response in pruritus is highly variable.
- Ondansetron via CSCI is stated to be *chemically* and *physically* compatible with alfentanil, dexamethasone, diamorphine, fentanyl, glycopyrronium, hydromorphone, metoclopramide, midazolam, and morphine sulfate.[3]
- Ondansetron via CSCI is stated to be *physically* compatible with octreotide and oxycodone.[3]

Pharmacology

Ondansetron is a selective 5-HT_3 receptor antagonist, blocking serotonin peripherally on vagal nerve terminals and centrally in the CTZ. It is particularly useful in the treatment of nausea/vomiting associated with serotonin release (e.g. damage to enterochromaffin cells due to bowel injury, chemotherapy, or radiotherapy).

References

1. Currow DC, Coughlan M, Fardell B, Cooney NJ. Use of ondansetron in palliative medicine. *J Pain Symptom Manage*. 1997;**13**(5):302–7.
2. Jones EA. Pruritus and fatigue associated with liver disease: is there a role for ondansetron? *Expert Opin Pharmacother*. 2008;**9**(4):645–51.
3. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Oxybutynin

Standard-release

Ditropan® (POM)
Tablet (scored): 2.5mg (84); 5mg (84).

Generic (POM)
Tablet: 2.5mg (56; 84); 3mg (56); 5mg (56; 84).
Oral solution: 2.5mg/5mL (150mL); 5mg/5mL (150mL).

Modified-release

Lyrinel® XL (POM)
Tablet: 5mg (30); 10mg (30).

Kentera® (POM)
Transdermal patch: 3.9mg/24 hours (applied for 72–96 hours).

Indications

- Urinary incontinence.
- Urinary frequency.

Contraindications and cautions

- Oxybutynin is contraindicated for use in patients with:
  - bladder outflow obstruction (that may precipitate urinary retention)
  - colostomy
  - GI obstruction
  - ileostomy
  - myasthenia gravis
  - narrow-angle glaucoma
  - severe ulcerative colitis
  - toxic megacolon.
- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients (see ➔ *Dose adjustments*, p. 526).
- Oxybutynin should be used with caution in the following:
  - autonomic neuropathy (such as in those with Parkinson's disease)
  - cardiac disease (e.g. arrhythmia, congestive heart failure, coronary heart disease, hypertension—risk of tachycardia)
  - dementia
  - GI reflux disease
  - hepatic impairment
  - hyperthyroidism (risk of tachycardia)
  - prostatic hypertrophy
  - pyrexia (reduces sweating)
  - renal impairment
  - ulcerative colitis.
- Monitoring is recommended, especially in the first few months after initiating therapy or increasing the dose due to the risk of CNS effects such as agitation, confusions, drowsiness, and hallucinations.

- Patients should be advised to seek advice if they develop a sudden loss of visual acuity or ocular pain (risk of narrow-angle glaucoma).
- Regular dental check-ups are advisable during long-term treatment due to the risk of oral complications caused by reduced salivary secretions (e.g. dental caries, oral candidosis).
- Oxybutynin may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: application site reaction (patch); dry mouth.
- *Common*: abdominal pain; constipation; diarrhoea; dizziness; drowsiness; dry eye; dry skin; dysgeusia; dyspepsia; dysuria; facial flushing; fatigue; flatulence; gastro-oesophageal reflux disease; headache; nausea; palpitations; pruritus; reduced sweating; urinary retention; urinary tract infection; visual disturbance (blurred vision).
- *Uncommon*: agitation; anorexia; decreased appetite; arrhythmia; confusion; convulsions; dysphagia; fluid retention; glaucoma; hallucinations; hypersensitivity; hypertension; memory impairment; nasal congestion; tachycardia; thirst; urticaria; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized by CYP3A4. *In vitro* data suggest it may have weak to moderate CYP2C8 and CYP2D6 inhibitory effects. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- The effect of grapefruit juice on the bioavailability of oxybutynin is unknown.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Bethanechol*—antagonism of effect.
- *Donepezil*—effect may be reduced.
- *β_2-agonists*—increased risk of tachycardia.
- *Cyclizine*—increased risk of anticholinergic adverse effects.
- *Domperidone*—may inhibit the prokinetic effect.
- *Galantamine*—effect may be reduced.
- *Laxatives*—effect may be reduced.
- *Metoclopramide*—may inhibit the prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *Rivastigmine*—effect may be reduced.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

Standard-release

- Initial dose 2.5mg PO TDS or 5mg PO BD. Can be increased, as necessary, up to a maximum dose of 5mg PO QDS.

Modified-release

- Patients may be transferred from the standard-release product.
- Initial dose 5mg PO OD. The dose can be increased after at least 1 week to 10mg PO OD. The dose can be further increased, at weekly intervals, to a maximum of 20mg PO OD.
- Alternatively, a 3.9mg transdermal patch can be applied twice weekly (every 3–4 days). The patch should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be used for each new patch and the same site should not be used within 7 days.

Dose adjustments

Elderly

- For the standard-release formulations, manufacturers recommend lower initial doses (e.g. 2.5mg PO BD), as elderly patients are more susceptible to adverse effects. In particular, the elderly may have an increased risk of cognitive decline and dementia.

Hepatic/renal impairment

- No specific guidance available. Use the lowest effective dose.

Additional information

- Plasma concentration of oxybutynin declines within 1–2 hours after removal of the transdermal patch.
- For *Lyrinel® XL*, the tablet membrane may pass through the GI tract unchanged.
- Standard-release tablets can be dispersed in water immediately prior to use if necessary (oral solution would be preferable).

Pharmacology

Oxybutynin is an anticholinergic drug that competitively antagonizes acetylcholine at post-ganglionic sites, including smooth muscle, secretary glands, and CNS sites. It is extensively metabolized by the liver, primarily by CYP3A4; there is an active metabolite, N-desethyloxybutynin, which has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin.

Oxybutynin is a racemic (50:50) mixture of R- and S-isomers. The pharmacological activity of oxybutynin resides predominantly in the R-isomer. R-oxybutynin shows greater selectivity for M_1 and M_3 muscarinic subtypes (predominant in the bladder detrusor muscle and parotid gland), compared to the M_2 subtype (predominant in cardiac tissue).

Oxycodone

Standard-release

OxyNorm® (CD2 POM)
Capsule: 5mg (*orange/beige*—56); 10mg (*white/beige*—56); 20mg (*pink/beige*—56).
Oral solution (sugar-free; alcohol-free): 5mg/5mL (250mL); 10mg/mL (120mL).
Injection: 10mg/mL (5); 20mg/2mL (5); 50mg/mL (5).

Generic (CD2 POM)
Capsule: 5mg (56); 10mg (56); 20mg (56).
Tablet: 5mg (56); 10mg (*scored;* 56); 20mg (*scored;* 56).
Oral solution (sugar-free; alcohol-free): 5mg/5mL (250mL); 10mg/mL (120mL).
Injection: 10mg/mL (5; 10); 20mg/2mL (5; 10); 50mg/mL (5; 10).

12-hourly modified-release

OxyContin® (CD2 POM)
Tablet: 5mg (*blue*—28); 10mg (*white*—56); 15mg (grey—56); 20mg (*pink*—56); 30mg (*brown*—56); 40mg (*yellow*—56); 60mg (*red*—56); 80mg (*green*—56); 120mg (*purple*—56).

Generic (CD2 POM)
Tablet: 5mg (28); 10mg (56); 15mg (56); 20mg (56); 30mg (56); 40mg (56); 60mg (56); 80mg (56); 120mg (56).

24-hourly modified-release

Onexila® XL (CD2 POM)
Tablet: 10mg (28); 20mg (28); 40mg (28); 80mg (28).

With naloxone

(See ➔ Chapter 3, *Naloxone*, p. 486).

Modified-release

Targinact® (CD2 POM)
Tablet: oxycodone 5mg/naloxone 2.5mg (28); oxycodone 10mg/naloxone 5mg (56); oxycodone 20mg/naloxone 10mg (56); oxycodone 40mg/naloxone 20mg (56).

Indications

- Moderate to severe pain in patients with cancer.
- Severe pain requiring the use of a strong opioid.
- Post-operative pain (*Targinact®*—not discussed).
- Second-line treatment of severe to very severe idiopathic restless legs syndrome (*Targinact®*—not discussed).

Contraindications and cautions

- If the dose of an opioid is titrated correctly, it is generally accepted that there are no absolute contraindications to the use of such drugs in palliative care, although there may be circumstances where one opioid is favoured over another (e.g. renal impairment, constipation).

Nonetheless, the SmPC states that oxycodone is contraindicated for use in patients with:
- acute abdomen
- asthma (severe)
- chronic constipation
- COPD (severe)
- cor pulmonale
- delayed gastric emptying
- hypercarbia
- moderate to severe hepatic impairment
- paralytic ileus
- respiratory depression with hypoxia.

- While no specific interaction has been observed, the SmPC cautions against concurrent administration with MAOIs or within 2 weeks of their discontinuation. If concomitant use is unavoidable (e.g. *linezolid*), ensure there are facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- There have been rare case reports of opioid analgesics being involved in serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when co-administered with other serotonergic medications such as MAOIs (see above), SSRIs, SNRIs, and TCAs (see ➔ *Drug interactions*, p. 530). Of the opioids, *morphine* is believed to carry the lowest risk, although oxycodone can be considered an alternative in this situation (NB—concurrent use with a MAOI is *not* a contraindication for oxycodone, unlike other opioids, e.g. *morphine*, *fentanyl*). Nonetheless treatment must be reviewed urgently if symptoms develop, morphine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of oxycodone and benzodiazepines (or *zopiclone/zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution in the following instances:
  - alcoholism
  - Addison's disease (adrenocortical insufficiency)
  - concurrent use of CNS depressants or MAOIs (see ➔ *Drug interactions*, p. 530)
  - delirium tremens
  - diseases of the biliary tract
  - elderly patients
  - head injury (risk of raised intracranial pressure)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 532)
  - history of alcohol and drug abuse
  - hypotension

- hypothyroidism
- hypovolaemia
- inflammatory bowel disorders
- pancreatitis
- prostatic hypertrophy
- raised intracranial pressure
- renal impairment (see ➔ *Dose adjustments*, p. 532)
- severe pulmonary disease (respiratory effects of opioids are more pronounced during sleep)
- toxic psychosis.

- Oxycodone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Avoid abrupt withdrawal as the development of physical and/or psychological dependence can occur within 2 weeks of continual use. An abstinence syndrome may be precipitated if oxycodone is suddenly discontinued; it may occur within a few hours after withdrawal and is maximal between 1 and 3 days. Withdrawal symptoms include:
  - abdominal colic
  - anxiety
  - body aches
  - diarrhoea
  - dysphoria
  - flu-like symptoms
  - irritability
  - mydriasis
  - nausea
  - restless legs syndrome
  - tachycardia
  - tremors.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see ➔, Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. Strong opioids tend to cause similar adverse effects, albeit to varying degrees.

- *Very common*: constipation (not *Targinact*®); dizziness; headache; nausea; pruritus; somnolence; vomiting.

- *Common*: abdominal pain; abnormal dreams/thoughts; anxiety; reduced appetite; asthenia; bronchospasm; confusional state; decreased cough; depression; diarrhoea; dry mouth; dyspepsia (give with food if problematic); dyspnoea; hyperhidrosis; insomnia; lethargy; rash; tremor.
- *Uncommon*: agitation; amnesia; biliary colic; convulsions (particularly in patients with epilepsy); dehydration; disorientation; drug withdrawal syndrome; dysgeusia; dysphagia; dysphoria; eructation; exfoliative dermatitis; euphoria; facial flushing; flatulence; gastritis; hallucinations; hiccups; hypersensitivity; hypertonia; hypoaesthesia; hypotonia; ileus; involuntary muscle contractions; elevated LFTs; miosis; palpitations (in context of withdrawal); paraesthesia; peripheral oedema; pyrexia; respiratory depression; restlessness; sexual dysfunction (erectile dysfunction, hypogonadism, loss of libido); speech disorder; supraventricular tachycardia; syncope; thirst; tolerance (to analgesic effect); ureteral spasm; urinary retention; vasodilation; vertigo.
- *Rare*: hypotension; postural hypotension; urticaria.
- *Unknown*: aggression; amenorrhoea; anaphylaxis; cholestasis; dental caries; hyperalgesia; sensorineural hearing loss and tinnitus (associated with toxicity).

Drug interactions

Pharmacokinetic

- Is a major substrate of CYP3A4 (noroxycodone—inactive); is a minor substrate of CYP2D6 (oxymorphone—active). Oxycodone is also a substrate of UGT2B7 and UGT2B4. Subsequent metabolism of noroxycodone and oxymorphone involves CYP3A4, CYP2D6, and glucuronidation by UGT2B7. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- The clinical significance of co-administration with CYP3A4 inhibitors (see ➔ *Inhibitors* on the inside back cover) is unknown. Clinical reports are lacking; in theory, this interaction may lead to an increased risk of toxicity due to possible increases in the plasma concentration of oxycodone and an increase in metabolism by CYP2D6 to the active metabolite oxymorphone. Dose adjustments may be necessary.
- Co-administration of *both* CYP3A4 and CYP2D6 inhibitors can *substantially increase* the effect of oxycodone.
- *Clarithromycin*—has been reported to increase exposure to oxycodone (opioid toxicity).
- *Miconazole*—has been shown to increase exposure to oral oxycodone.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of oral oxycodone through inhibition of intestinal CYP3A4.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).

- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 527.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing affect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of morphine may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *MAOIs*—risk of severe and unpredictable interactions with MAOIs, involving the potentiation of opioid or serotonergic effects.
- *Serotonergic drugs (e.g. SNRIs, SSRIs)*—risk of serotonin toxicity.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 527.

Dose

Note that it is generally accepted that PRN doses may be given every 2–4 hours (some centres suggest a maximum daily limit of six doses, irrespective of indication). In the case of severe pain or end-of-life care, PRN doses may be given as frequently as every hour under specialist supervision.

The initial dose of oxycodone depends upon the patient's previous opioid requirements. Refer to ➔ Chapter 2, *Equianalgesia and opioid switch*, p. 56 for information regarding opioid dose equivalences. Refer to ➔ Chapter 2, *Breakthrough cancer pain*, p. 54 for guidance relating to BTcP.

Note that the shell of the modified-release tablet may be present in faeces, which has no clinical relevance.

Oral

Standard-release

- For opioid-naïve patients, initial dose is 2.5mg to 5mg PO every 4–6 hours PRN (or more frequently, as described above). The dose is then increased, as necessary, until a stable dose is attained. The patient should then be converted to a modified-release formulation.

Modified-release

- For opioid-naïve patients, initial dose is 5mg to 10mg PO BD. The dose can then be titrated as necessary.

Onexila® XL

- Initial dose for opioid-naïve patients is 10mg PO OD. Maximum licensed daily dose is 400mg.

Targinact®

- For opioid-naïve patients, initial dose is 10mg/5mg of oxycodone/naloxone PO BD. This can be titrated (using immediate-release oxycodone preparations), as necessary, to the maximum licensed dose of 80mg/40mg PO BD.

- For doses >80mg/40mg PO BD, use of additional modified-release oxycodone is suggested.
- The 5mg/2.5mg oxycodone/naloxone formulation is not licensed for initiation of treatment, only for subsequent dose titration.

Subcutaneous

- Initial dose in opioid-naïve patients is 2.5mg to 5mg SUBCUT every 4–6 hours PRN (or more frequently, as described above).
- Alternatively, 5mg to 10mg via CSCI over 24 hours and increase as necessary.

Dose adjustments

Elderly

- Usual adult doses can be used, although lower doses in opioid-naïve patients may be preferable (see below). Dose requirements should be individually titrated.

Hepatic/renal impairment

- In patients with mild hepatic impairment, the plasma concentration is expected to be increased. Lower doses and increased dosing interval may be needed. The starting dose is suggested to be 1.25mg to 2.5mg PO every 4–6 hours PRN (or more frequently, as described above) and titrated to pain relief. The SmPC states patients with severe hepatic impairment should be closely monitored (i.e. the dose should be titrated carefully to the patient's need).
  - One manufacturer contraindicates the use of oxycodone in patients with moderate to severe hepatic impairment.
  - *Targinact®* must be used with caution in patients with mild hepatic impairment, as both oxycodone and naloxone concentrations may be elevated (the SmPC states naloxone concentrations are affected to a higher degree than oxycodone; this *may* impact pain control).
  - *Targinact®* is contraindicated for use in patients with moderate to severe hepatic impairment.
- Despite the UK SmPC contraindication, *hydromorphone* may be the preferred opioid in hepatic impairment.
- In patients with renal impairment, the plasma concentration of oxycodone is likely to be increased. The initial dose is suggested to be 1.25mg to 2.5mg PO every 4–6 hours PRN (or more frequently, as described above) and titrated carefully to pain relief.
  - *Targinact®* must be used with caution in patients with renal impairment, as both oxycodone and naloxone concentrations may be elevated (the SmPC states naloxone concentrations are affected to a higher degree than oxycodone; this may impact pain control).
- If patients with hepatic and/or renal impairment are switched from another opioid to oxycodone, clinical judgement must be used as empirical dose adjustments representing a 33–50% reduction of usual equianalgesic doses may be needed.
- In patients established on oxycodone, with subsequent development of hepatic or renal impairment, an empirical dose reduction may be required.

Additional information

- If other analgesic measures are introduced—pharmacological or other alternatives, e.g. radiotherapy—the dose of oxycodone may need to be reduced.
- *OxyNorm*® 10mg/mL oral solution may be mixed with a soft drink to improve taste.
- *OxyNorm*® 5mg/5mL and 10mg/mL oral solutions do not contain alcohol as an excipient.
- Ultrarapid metabolizers of CYP2D6 may be at risk of toxicity due to the potential increase in formation of the active metabolite oxymorphone.
- Oxycodone is stated to be *chemically* and *physically* compatible under stated conditions with dexamethasone, glycopyrronium, haloperidol, hyoscine butylbromide, hyoscine hydrobromide, ketamine, levomepromazine, metoclopramide, and midazolam. There is a concentration-dependent compatibility issue with cyclizine; unlike diamorphine, the exact concentrations have not yet been identified. Oxycodone is stated to be *physically* compatible under stated conditions with clonazepam, ketorolac, octreotide, ondansetron, and ranitidine.[2]

Pharmacology

Oxycodone is a strong opioid with similar properties to morphine and acts primarily via MORs, although it is also stated to have affinity for DORs and KORs (the clinical significance of this has yet to be realized). Oxycodone has weak anticholinergic activity and may have a weak serotonin reuptake inhibitory effect. Following oral administration, oxycodone is well absorbed, with a bioavailability of up to 87%. It is metabolized principally to the inactive metabolite noroxycodone by CYP3A4 (approximately 45% of a dose). A minor metabolic pathway involves CYP2D6, with the active metabolite oxymorphone being produced (approximately 19% of a dose). Oxycodone can undergo direct glucuronidation by UGT2B7 and UGT2B4; this pathway is likely to become more relevant if CYP3A4 and CYP2D6 are inhibited (or just CYP3A4 in a CYP2D6 poor metabolizer). Subsequent metabolism of oxymorphone involves CYP3A4, CYP2D6, and conjugation via UGT2B7. In general, the contribution of oxymorphone to the overall analgesic benefit of oxycodone is minimal, since it is generally present in the plasma at low concentrations. However, ultrarapid CYP2D6 metabolizers or patients receiving CYP3A4 inhibitors can respond to oxycodone at lower-than-expected doses. Approximately 10% of oxycodone is excreted unchanged, which may accumulate in patients with renal impairment.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
2. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Pamidronate disodium

Generic (POM)

Injection (concentrate solution):

3mg/mL: 5mL vial (15mg); 10mL vial (30mg); 20mL vial (60mg); 30mL vial (90mg).

6mg/mL: 10mL vial (60mg).

9mg/mL: 10mL vial (90mg).

15mg/mL: 1mL amp (15mg); 2mL amp (30mg); 4mL amp (60mg); 6mL amp (90mg).

Indications

- Tumour-induced hypercalcaemia.
- Bone pain and osteolytic lesions due to metastases associated with breast cancer or multiple myeloma.
- Paget's disease of bone (*not discussed*).

Contraindications and cautions

- Pamidronate must be given as an infusion, and not as a bolus injection. All preparations should be diluted in a calcium-free infusion solution (NaCl preferred).
- Assess renal function and electrolytes (e.g. Ca^{2+}, Mg^{2+}) before each dose, and ensure adequate hydration (especially if treating hypercalcaemia).
- Use with caution in the following circumstances:
  - cardiac disease (risk of fluid overload)
  - elderly
  - patients who have undergone thyroid surgery (risk of hypocalcaemia if hypoparathyroidism)
  - renal impairment (see ➔ *Dose adjustments*, p. 536)
  - severe hepatic impairment (see ➔ *Dose adjustments*, p. 536).
- Assess the need for calcium and vitamin D supplements in patients receiving pamidronate other than for hypercalcaemia.
- Consider dental examination before initiating repeated infusions of pamidronate due to the possibility of inducing osteonecrosis of the jaw (see ➔ *Adverse effects*)

☹ Adverse effects

Osteonecrosis of the jaw is a potential complication of bisphosphonate therapy. It has been reported in cancer patients and in many who had a pre-existing local infection or a recent extraction. Cancer patients are more likely to be at risk of osteonecrosis as a result of their disease, cancer therapies, and blood dyscrasias. Dental examination is recommended for patients undergoing repeated infusions of pamidronate (and other bisphosphonates), and dental surgery should be avoided during this treatment period as healing may be delayed.

Severe, and occasionally incapacitating, bone, joint, and/or muscle pain has been reported with bisphosphonate use. Time to onset varies from 1 day to several months after initiation of treatment, but symptoms

should improve upon discontinuation. Some patients will develop the same symptoms upon subsequent treatment with pamidronate or another bisphosphonate.

Atypical femoral fractures have been reported with bisphosphonate therapy. Although a rare occurrence, during bisphosphonate treatment, patients should be advised to report any new thigh, hip, or groin pain.

Refer to the SmPC for a full list of adverse effects.

- *Very common*: fever (within 48 hours of treatment; sometimes with rigor, fatigue, and flushes); hypocalcaemia; hypophosphataemia.
- *Common*: abdominal pain; anaemia; anorexia; arthralgia; conjunctivitis; constipation; diarrhoea; drowsiness; gastritis; generalized pain; headache; hypertension; hypokalaemia; hypomagnesaemia; insomnia; infusion site reactions; lymphocytopenia; myalgia; nausea; raised SeCr; rash; somnolence; symptomatic hypocalcaemia (paraesthesia, tetany); transient bone pain; thrombocytopenia; vomiting.
- *Uncommon*: abnormal LFTs; acute renal failure; agitation; dizziness; dyspepsia; hypotension; lethargy; muscle cramps; osteonecrosis; pruritus; raised serum urea; seizures; uveitis.
- *Rare*: focal segmental glomerulosclerosis, including the collapsing variant; nephrotic syndrome.
- *Very rare*: acute respiratory distress syndrome; anaphylactic shock; confusion; congestive heart failure due to fluid overload; deterioration of pre-existing renal disease; episcleritis; glomerulonephropathy; haematuria; hyperkalaemia; hypernatraemia; interstitial lung disease; left ventricular failure (dyspnoea, pulmonary oedema); leucopenia; osteonecrosis of the external auditory canal; reactivation of herpes simplex and herpes zoster; renal tubular disorder; scleritis; tubulointerstitial nephritis; visual hallucinations; xanthopsia.
- *Unknown*: atrial fibrillation; orbital inflammation; osteonecrosis of the jaw.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None known.

Pharmacodynamic

- *Aminoglycosides*—may have additive hypocalcaemic effect.
- *Diuretics*—increased risk of renal impairment.
- *NSAIDs*—increased risk of renal impairment.
- *Thalidomide*—increased risk of renal impairment (in treatment of multiple myeloma).

Dose

Tumour-induced hypercalcaemia

- Ensure patients are well hydrated prior to, and following, administration of pamidronate.

- The dose of pamidronate depends on the patient's initial serum Ca^{2+} levels (see Table 3.16). The dose is usually infused as a single dose.
- Must be given as an IVI at a rate not exceeding 1mg/min.

Table 3.16 Pamidronate dose according to serum calcium

Initial serum calcium (mmol/L)	Recommended dose (mg)
Up to 3.0	15–30
3.0–3.5	30–60
3.5–4.0	60–90
Above 4.0	90

Osteolytic lesions and bone pain

- 90mg by IVI at a rate not exceeding 1mg/min every 4 weeks.
- Note that calcium 500mg and vitamin D 400 units should also be taken daily.

Dose adjustments

Elderly

- Usual adult doses can be used.

Hepatic/renal impairment

- Dose adjustment is unnecessary in patients with mild to moderate hepatic impairment. The manufacturer advises caution in patients with severe hepatic impairment due to lack of data.
- For the treatment of osteolytic lesions, if renal function deteriorates, treatment should be withheld until renal function returns to within 10% of the baseline value.
- For the treatment of hypercalcaemia, dose adjustment is unnecessary in patients with mild to moderate renal impairment (CrCl >30mL/min). In severe renal impairment (CrCl <30mL/min), treatment should only be administered if benefit outweighs the potential risk. A lower dose of 30mg may produce normocalcaemia.[1] In these patients, the infusion rate should not exceed 90mg/4 hours (or 22mg/hr). Note the SmPC states pamidronate should not be administered to patients with severe renal impairment (CrCl <30mL/min) unless in the case of life-threatening tumour-induced hypercalcaemia where the benefit outweighs the potential risk.

Additional information

- The concentrate solution should be diluted to a maximum concentration of 90mg/250mL with infusion fluid (NaCl or GLU).
- Corrected serum Ca^{2+} = actual serum Ca^{2+} + [(40 − serum albumin g/L) × 0.02].
- In the treatment of hypercalcaemia, serum Ca^{2+} levels should not be measured until 5–7 days post-dose. A significant decrease in serum Ca^{2+} concentration is generally observed 24–48 hours after administration of pamidronate, with a median time to normalization of 3–7 days and

normalization in 70% of patients within 7 days. Seek specialist advice, should the corrected serum Ca^{2+} concentration not return to normal after 7–10 days; a second dose of pamidronate can be given 7–10 days after the initial dose in such patients.
- The onset of treatment effect for skeletal-related events is 2–3 months.
- Relief from bone pain may occur within 14 days, although it may be up to 3 months before the maximum effect is seen.

Pharmacology

Pamidronate disodium is an inhibitor of osteoclastic bone resorption. It has been shown to exert its activity by binding strongly to hydroxyapatite crystals, inhibiting their formation and dissolution and suppressing the accession of osteoclast precursors onto bone. Additionally, and to a greater extent, as the drug binds to bone mineral, this reduces the resorption of osteoclastic bone. It is almost exclusively excreted unchanged by the kidney.

Reference

1. Norman SJ, Reeves DJ, Saum LM. Use of pamidronate for hypercalcemia of malignancy in renal dysfunction. *J Pharm Pract.* 2021;**34**(4):553–7.

Pantoprazole ♡

Protium® (POM)
Injection: 40mg.

Generic (POM)
Tablet: 20mg (28); 40mg (28).
Injection: 40mg.

NB—pantoprazole 20mg tablets can be sold OTC for short-term treatment of reflux symptoms (e.g. heartburn) in adults aged over 18 years; maximum daily dose 20mg PO for a maximum of 4 weeks (P).

Pantoloc Control (P)
Tablet: 20mg (14).

Indications

- Treatment of gastric and duodenal ulcers.
- Treatment of gastro-oesophageal reflux disease.
- Treatment of severe oesophagitis.
- Treatment of mild reflux disease and associated symptoms.
- Long-term treatment and prevention of relapse in reflux oesophagitis.
- Prophylaxis and treatment of NSAID-associated peptic ulcer disease.
- Zollinger–Ellison syndrome (and other hypersecretory conditions).

Contraindications and cautions

- Increased gastric pH resulting from pantoprazole treatment may critically affect the absorption of certain drugs (see ➔ *Drug interactions*, p. 539).
- Treatment with pantoprazole may lead to a slightly increased risk of developing GI infections (e.g. *Clostridium difficile*). Therefore, avoid unnecessary use or high doses.
- The SmPC recommends monitoring of LFTs in patients with severe hepatic impairment who are on long-term treatment.
- Rebound acid hypersecretion may occur on discontinuation if the patient has received >8 weeks' treatment.
- Pantoprazole is predominantly metabolized by CYP2C19, and CYP3A4 to a lesser extent. Factors affecting CYP2C19 activity, such as phenotype (see Box 1.3) and drugs (see ➔ *Drug interactions*, p. 539), can alter response and adverse effects.
- PPIs are associated with a range of electrolyte disturbances such as hyponatraemia and hypomagnesaemia (and associated hypocalcaemia and hypokalaemia). Suspect the PPI, should unexplainable symptoms present (e.g. confusion, delirium, generalized weakness, nausea). The effect on Na^+ metabolism is unclear, possibly involving ADH. PPIs may reduce active Mg^{2+} absorption in the small intestine by affecting function of a transient receptor protein channel. Poor metabolizer status may contribute to such adverse effects.
- There is a *conditional* risk of QT prolongation/TdP due to the propensity to cause significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia). Monitor electrolytes regularly in

patients with known QT interval prolongation or congenital long QT syndrome and in those taking drugs that prolong the QT interval (see *Drug interactions*).
- When used in high doses and over long durations (>1 year), PPIs may increase the risk of hip, wrist, and spine fracture, predominantly in the elderly or in the presence of other recognized risk factors. Consider the need for adequate vitamin D and calcium intake.
- Pantoprazole may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

- *Uncommon*: abdominal distension; abdominal discomfort and pain; altered LFTs; constipation; diarrhoea; dizziness; dry mouth; fatigue; flatulence; fracture of the hip, wrist, or spine; headache; nausea/vomiting; pruritus; rash; sleep disorders.
- *Rare*: agranulocytosis; angioedema; arthralgia; depression; gynaecomastia; hyperlipidaemia; hypersensitivity; myalgia; peripheral oedema; raised serum bilirubin; raised body temperature; taste disorders; urticaria; visual disturbances; weight changes.
- *Very rare*: disorientation; leucopenia; pancytopenia; thrombocytopenia.
- *Unknown*: confusion; hallucinations; hepatocellular injury; hepatocellular failure; hepatitis; hypokalaemia; hypomagnesaemia; hyponatraemia; interstitial nephritis; jaundice; Stevens–Johnson syndrome; subacute cutaneous lupus erythematosus.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Pantoprazole is metabolized by CYP2C19; a minor pathway involves CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- The clinical significance of co-administration with CYP2C19/CYP3A4 inducers or inhibitors (see *Inducers* and *Inhibitors* on the inside back cover) is unknown. The prescriber should be aware of the potential for interactions and that dosage adjustments may be necessary.
- Drugs with pH-dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced

  - *ferrous sulfate*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g. 100mg) at the same time as ferrous sulfate to improve absorption
  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations
  - *metronidazole suspension*—pantoprazole may reduce/prevent the absorption of metronidazole.
- *Fluconazole*—may cause increased pantoprazole concentrations (CYP2C19 inhibition).
- *Methotrexate*—pantoprazole may cause increases in levels of methotrexate; consider withholding pantoprazole.

Pharmacodynamic
- Pantoprazole may cause prolongation of the QT interval due to the propensity to cause electrolyte disturbances. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Corticosteroids*—concurrent use may increase the risk of osteoporosis and osteoporotic fractures.

Dose

Treatment of duodenal and gastric ulcers
- 40mg PO OM for 2–4 weeks (duodenal) or 4–8 weeks (gastric).
- Alternatively, 40mg IV OD until oral treatment is possible.

Treatment of gastro-oesophageal reflux disease
- 40mg PO OM for 4–8 weeks (gastric).
- Alternatively, 40mg IV OD until oral treatment is possible.

Treatment of severe oesophagitis
- 40mg PO OM for 8 weeks, can be continued as maintenance treatment if appropriate, or increased to 40mg BD if treatment ineffective.

Treatment of mild reflux disease and associated symptoms
- 20mg PO OM for 2–8 weeks. After this time, patients can be controlled with 20mg PO OD PRN, switching to regular treatment if necessary.

Long-term treatment and prevention of relapse in reflux oesophagitis
- 20mg to 40mg PO OM.

Prophylaxis of NSAID-associated peptic ulcer disease
- 20mg PO OM.

Treatment of Zollinger–Ellison syndrome (and other hypersecretory conditions)
- Initially 80mg PO OM and adjusted according to response. Maximum per dose of 80mg.
- Alternatively, 80mg IV OM (or 160mg in two divided doses if rapid acid control required), then 80mg IV OM (maximum per dose 80mg) and adjusted according to response.

Dose adjustments

Elderly

- Dose adjustments are not necessary in the elderly.

Hepatic/renal impairment

- In patients with severe liver impairment, 20mg OM should not be exceeded and regular LFTs should be performed.
- No dose adjustments are necessary in renal impairment.

Additional information

- Tablets should not be chewed or crushed but should be swallowed whole.

Pharmacology

Pantoprazole is a gastric PPI, reducing the release of H^+ from parietal cells by inhibiting H^+/K^+ ATPase. It is rapidly inactivated by gastric acid; hence oral formulations are enteric-coated. It is extensively metabolized, mainly by CYP2C19, although an alternative pathway involves CYP3A4. Note that CYP2C19 poor metabolizers (or patients taking CYP2C19 inhibitors) can have significantly higher plasma concentrations, leading to unexpected results. Metabolites are virtually inactive and are eliminated mainly by renal excretion, with a small percentage eliminated in faeces.

Paracetamol

Perfalgan® (POM)
IV infusion: 500mg/50mL (12); 1g/100mL (12).

*Generic (POM)**
Tablet: 500mg (16; 32; 100).
Caplet: 500mg (16; 32; 100).
Effervescent tablet: 500mg (24; 60; 100); 1g (50).
Soluble tablet: 500mg (60).
Oral suspension: 250mg/5mL (100mL); 500mg/5mL (300mL).
NB—sugar-free suspensions are available.
Suppository: 250mg (10); 500mg (10); 1g (10).
IV infusion: 100mg/10mL (20); 500mg/50mL (10); 1g/100mL (10; 20).

Combination products

See codeine (see ➔ Chapter 3, *Codeine*, p. 177), *dihydrocodeine* (see ➔ Chapter 3, *Dihydrocodeine*, p. 223), *and tramadol* (see ➔ Chapter 3, *Tramadol*, p. 662).

Indications

- Mild to moderate pain.
- Pyrexia.
- Short-term treatment of moderate pain (IV).

Contraindications and cautions

- Paracetamol is contraindicated for use in severe hepatic impairment.
- It should be used with caution in patients with:
  - alcohol dependence
  - concurrent use of enzyme-inducing drugs (see ➔ *Drug interactions*)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 543)
  - renal impairment (see ➔ *Dose adjustments*, p. 543)
  - state of malnutrition (low reserves of hepatic glutathione).

☹ Adverse effects

- *Rare*: abnormal LFTs; hypotension (on infusion).
- *Very rare*: blood dyscrasias.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Major route of metabolism is conjugation via glucuronidation through UGT1A6 and UGT1A9, and sulfation. Minor routes of metabolism involve UGT1A1, UGT2B15, CYP2E1, CYP1A2, CYP2D6, and CYP3A4. With higher doses, conjugation pathways become saturated and CYP2E1 becomes the predominant pathway.

* *The legal status of paracetamol depends upon pack size: 16 (GSL), 32 (P), >100 (POM).*

- *Alcohol*—acute effect inhibits CYP2E1; chronic effect induces CYP2E1, although it is unclear if the risk of toxicity rises.
- *Carbamazepine*—increased risk of paracetamol toxicity (especially in overdose).
- *Colestyramine*—absorption of paracetamol is reduced (avoid co-administration by 2 hours).
- *Imatinib*—the SmPC cautions high doses of imatinib (UGT1A1 inhibitor) and paracetamol glucuronidation.
- *Metoclopramide*—increased rate of absorption of paracetamol.
- *Warfarin*—monitor with long-term paracetamol therapy as INR may be raised.

Pharmacodynamic

- None known.

Dose

For pain and fever

- 0.5g to 1g PO or PR up to every 4–6 hours. Maximum dose of 4g in 24 hours.
- Alternatively, if necessary, by IVI:
  - for adults >50kg, give 1g every 4–6 hours; maximum dose of 4g in 24 hours
  - for adults <50kg, give 15mg/kg every 4–6 hours; maximum dose of 60mg/kg in 24 hours.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- Dose reductions may be necessary in mild to moderate liver impairment. Although contraindicated, maximum PO daily doses of <2g/day appear to be well tolerated. Close monitoring of treatment is recommended.
- The SmPC for IV paracetamol states the maximum daily dose must not exceed 3g/day in patients with hepatic impairment (NB—licensed for short-term use; if used more regularly, off-label, a maximum daily dose of 2g/day may be more appropriate). Avoid IV paracetamol in patients with severe hepatic impairment.
- For patients with severe renal impairment (CrCl <30mL/min), the dose interval of IV paracetamol should be increased to 6 hours.

Additional information

- Liver damage can occur with small increases of the dose above the 4g/day recommendation and so it is especially important to ensure that patients are not taking proprietary preparations, as well as prescribed paracetamol or combinations products.

Pharmacology

The precise analgesic action of paracetamol is unknown. Recent work suggests that paracetamol may be a pro-drug which undergoes metabolism to

form an active metabolite. This compound may produce analgesia through involvement of multiple systems, e.g. the TRPV1 receptor, serotonergic and cannabinoid pathways. When used regularly, it is an effective and useful analgesic, and it can be a useful adjunct with opioids.

Paracetamol is quickly absorbed after oral administration, with an approximate bioavailability of 80%. After rectal administration, its bioavailability is considerably lower, and absorption is often delayed and erratic. It is largely metabolized by conjugation (glucuronidation and sulfation) reactions in the liver by various UGTs—UGT1A1, UGT1A6 (major), UGT1A9 (major), and UGT2B15. Minor pathways involve various CYP enzymes. With higher doses, as conjugation reactions become saturated, the minor CYP routes of paracetamol metabolism (CYP2E1, in particular) become more important as a reactive intermediate, N-acetyl-p-benzoquinone imine (NAPQI) is formed. Usually, NAPQI is inactivated by conjugation with glutathione in the liver. However, following ingestion of a large amount of paracetamol, the hepatic stores of glutathione become depleted, so more NAPQI is available to cause hepatic damage and cellular death. Toxicity may occur following ingestion of approximately twice the normal daily dose (i.e. 14–16 tablets of 500mg paracetamol in an adult). Drugs that induce CYP1A2 and CYP2E1 may increase the risk of paracetamol toxicity.

Parecoxib ⚠

Dynastat® (POM)
Powder and solvent for solution for injection: 40mg (5).
Powder for solution for injection: 40mg (10).
NB—after reconstitution, the concentration of parecoxib is 20mg/mL.

Indications

- Short-term management of acute post-operative pain (*not discussed*).
- ✝Management of refractory cancer pain.[1]

Contraindications and cautions

- Contraindicated for use in patients with:
  - active GI bleeding or GI ulceration
  - congestive heart failure (NYHA classes II–IV)
  - established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease
  - history of previous serious allergic drug reaction of any type, especially cutaneous reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme
  - hypersensitivity reactions (e.g. asthma, nasal polyps, rhinitis) to ibuprofen, aspirin, or other NSAIDs (including COX-2 inhibitors)
  - hypersensitivity to sulphonamides
  - inflammatory bowel disease
  - severe hepatic dysfunction (serum albumin <25g/L or Child–Pugh score ≥10).
- A dose reduction may be necessary in the elderly (see ➔ *Dose adjustments*, p. 547).
- There is limited clinical experience with parecoxib beyond 3 days. Use the minimum effective dose for the shortest duration necessary in order to reduce the risk of cardiac and GI events. Treatment should be reviewed within *1 week* of initiation. In the absence of benefit, other options should be considered.
- Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease need careful consideration due to the increased risk of thrombotic events.
- Use with caution in the following circumstances:
  - concurrent use of diuretics, corticosteroids, and NSAIDs (see ➔ *Drug interactions*, p. 546)
  - congestive heart failure and/or left ventricular dysfunction; hepatic impairment (see ➔ *Dose adjustments*, p. 547)
  - hyperlipidaemia
  - hypertension (particularly uncontrolled)
  - oedema
  - renal impairment (see ➔ *Dose adjustments*, p. 547)
  - smoking (risk factor for CV and GI toxicity)
  - Type 1 and Type 2 diabetes (risk factors for CV events).
- Parecoxib may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).

- Patients known to be CYP2C9 poor metabolizers should be treated with caution; similarly, drugs that inhibit CYP2C9 should be used with caution (see ➔ *Drug interactions*). In both cases, the prescriber should consider reducing the dose to half the lowest recommended dose.
- Serious skin reactions (e.g. exfoliative dermatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported very rarely in association with the use of parecoxib. Patients appear to be at highest risk within the first month of treatment. Patients with a history of sulphonamide allergy may be at greater risk of serious skin reactions or hypersensitivity reactions. Discontinue treatment at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. Treatment with parecoxib must not be restarted.
- Consider co-prescription of misoprostol or a PPI if at high risk of NSAID-induced GI toxicity, e.g. long-term NSAID therapy, concurrent use of drugs that increase the risk of GI toxicity (see ➔ *Drug interactions*).
- Refer to ➔ Chapter 2, *Selection of an NSAID*, p. 49 for further information about selecting an NSAID.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: nausea.
- *Common*: abdominal pain; agitation; back pain; constipation; dizziness; dyspepsia; flatulence; hyperhidrosis; hypertension; hypokalaemia; hypotension; insomnia; oliguria; peripheral oedema; pruritus; vomiting.
- *Uncommon*: anorexia; arthralgia; asthenia; bradycardia; cerebrovascular disorder; dry mouth; ear pain; ecchymosis; gastroduodenal ulceration; gastro-oesophageal reflux disease; hyperglycaemia; hypertension (aggravated); injection site reaction; myocardial infarction; postural hypotension; PE; rash; thrombocytopenia; urticaria.
- *Rare*: acute renal failure; anaphylaxis; oesophagitis; oral oedema; pancreatitis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Parecoxib is a pro-drug and is rapidly metabolized to valdecoxib, which is a substrate of CYP2C9 and CYP3A4. It is a moderate inhibitor of CYP2C19 and CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Carbamazepine*—can reduce the effectiveness of parecoxib.
- *Clopidogrel*—antiplatelet action may be reduced.
- *Codeine*—possibly reduced analgesic benefit.
- *Digoxin*—monitoring of serum digoxin is recommended.

- *Fluconazole*—use half the recommended doses of parecoxib, as plasma concentration can be increased.
- *Haloperidol*—parecoxib may inhibit metabolism; possible increased risk of adverse effects.
- *Lithium*—parecoxib may reduce lithium renal excretion.
- *Miconazole*—may increase the effectiveness of parecoxib and risk of adverse effects.
- *Rifampicin*—can reduce the effectiveness of parecoxib.
- *Risperidone*—parecoxib may inhibit metabolism; possible increased risk of adverse effects.
- *Tamoxifen*—parecoxib may reduce metabolism, and therefore effectiveness.
- *Tramadol*—possibly reduced analgesic benefit.

Pharmacodynamic

- *ACE-Is/ARBs*—risk of AKI.
- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—reduced antihypertensive effect.
- *Antiplatelet drugs*—increased risk of GI ulceration or other GI complications.
- *Corticosteroids*—increased risk of GI toxicity.
- *Ciclosporin*—increased risk of nephrotoxicity.
- *Digoxin*—NSAIDs may exacerbate cardiac failure.
- *Diuretics*—increased risk of acute renal insufficiency (potential dehydration and/or hypovolaemia).
- *Opioids*—may have an opioid-sparing effect as the daily requirement for PRN opioids was significantly reduced when co-administered with parecoxib in clinical trials.
- *SSRIs*—increased risk of GI bleeding.

Dose

Gastroprotective treatment must be prescribed concurrently if appropriate. Consider misoprostol or a PPI if the oral route is available. Alternatively, ranitidine (if available) or esomeprazole via separate CSCI can be considered.

Dilute the CSCI to the largest possible volume with NaCl to reduce the risk of a site reaction.

[+]Management of cancer pain

- Initial dose 10mg to 20mg SUBCUT 6- to 12-hourly PRN, to a maximum of 80mg daily.
- Alternatively, 40mg OD via CSCI, increasing to a maximum dose of 80mg as necessary (but see *Dose adjustments*).

Dose adjustments

Elderly

- Dose adjustments are generally unnecessary in elderly patients (≥65 years). For elderly patients weighing <50kg, however, treatment should be initiated with half the usual recommended dose, and the maximum daily dose reduced to 40mg.

Hepatic/renal impairment

- Parecoxib is contraindicated for use in patients with severe hepatic impairment (serum albumin <25g/l or Child–Pugh score ≥10). Dose adjustments are not necessary in patients with mild hepatic impairment (Child–Pugh score 5–6). For patients with moderate hepatic impairment (Child–Pugh score 7–9), the initial dose should be 20mg (CSCI or SC), with a daily maximum of 40mg.
- Dose adjustments are not necessary for patients with mild to moderate renal impairment (CrCl 30 to 80mL/min). In patients with severe renal impairment (CrCl ≤30mL/min) or those who may be predisposed to fluid retention, the initial dose should be 20mg (CSCI or SUBCUT) and (if appropriate) the patient's renal function should be closely monitored.

Additional information

- Parecoxib is currently one of three NSAIDs that have reportedly been given via CSCI, with the other two being diclofenac and ketorolac.
- Analgesic efficacy with parecoxib is dose-related and it has been shown to have comparable efficacy to ketorolac in terms of post-operative analgesia. Parecoxib has little or no effect on platelet aggregation and has a reduced GI risk, compared with ketorolac.[2]
- Compatibility data are currently lacking and parecoxib should be infused via a separate CSCI. Nonetheless, anecdotal reports suggest that parecoxib is physically compatible with low-dose dexamethasone.[3]

Pharmacology

Parecoxib represents the first parenteral selective COX-2 inhibitor; it is a sulphonamide-containing pro-drug that is rapidly hydrolysed in the liver to the active compound valdecoxib. Valdecoxib undergoes extensive hepatic metabolism involving multiple pathways, including CYP3A4, CYP2C9, and glucuronidation. Parecoxib appears to be a CYP2C19 and CYP2D6 inhibitor. Less than 5% of unchanged valdecoxib is recovered in the urine, whereas no unchanged parecoxib is detected in the urine, with only trace amounts in the faeces. Valdecoxib was withdrawn in 2005 after safety concerns regarding serious skin reactions. Despite this, parecoxib remains available, although it is contraindicated for use in patients with hypersensitivity to sulphonamides and must be discontinued if signs of hypersensitivity manifest (see *Contraindications and cautions*, p. 545).

References

1. Armstrong P, Wilkinson P, McCorry NK. Use of parecoxib by continuous subcutaneous infusion for cancer pain in a hospice population. *BMJ Support Palliat Care*. 2018;**8**(1):25–9.
2. Harris SI, Kuss M, Hubbard RC, Goldstein JL. Upper GI safety evaluation of parecoxib sodium, a new parenteral cyclooxygenase-2-specific inhibitor, compared with ketorolac, naproxen, and placebo. *Clin Ther*. 2001;**23**(9):1422–8.
3. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Paroxetine ♡

Seroxat® (POM)
Tablet (scored): 10mg (28); 20mg (30); 30mg (30).

Generic (POM)
Tablet: 10mg (28); 20mg (30); 30mg (30); 40mg (28, 30).

Indications

- Anxiety.
- Major depression.
- Panic.
- ✝Pruritus.[1]

Contraindications and cautions

- Do not use with an irreversible MAOI, or within 14 days of stopping one, or at least 24 hours after discontinuation of a reversible MAOI (e.g. *moclobemide*, *linezolid*). Note that in exceptional circumstances, *linezolid* may be given with paroxetine, but there must be facilities for close observation and monitoring of BP and other symptoms of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- Although the combination of the selective MAO-B inhibitors *rasagiline* and *selegiline* with SSRIs is well tolerated, there have been case reports of serotonin toxicity. If such a combination is necessary, the recommendation is to use citalopram or sertraline without exceeding recommended doses.[2]
- There is a *conditional* risk of QT prolongation/TdP (CYP2D6 inhibition of drugs with QT/TdP risk).
- Serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) has been reported in patients using SSRIs. Paroxetine should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Paroxetine should not be used concomitantly with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 551).
- Use with caution in epilepsy. SSRIs are, however, considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.
- In addition, use with caution in:
  - diabetes (SSRIs can alter glycaemic control and may cause impaired awareness of hypoglycaemia)
  - elderly (greater risk of hyponatraemia)
  - hepatic/renal impairment (see ➔ *Dose adjustments*, p. 552)
  - glaucoma (may cause mydriasis).
- Akathisia/psychomotor restlessness may occur within the first few weeks of treatment (consider discontinuing).
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.

- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Co-administration with tamoxifen has been shown to reduce the plasma levels of the potent antioestrogen endoxifen. The precise clinical significance of this interaction is presently unknown, but the MHRA has advised co-administration of CYP2D6 inhibitors should be avoided (see *Drug interactions*, p. 551).
- Paroxetine may increase the risk of haemorrhage. Use with caution in patients with bleeding disorders or with concurrent use of other drugs carrying a similar risk (see *Drug interactions*, p. 551).
- Some patients may experience increased anxiety symptoms at the beginning of treatment. This paradoxical reaction usually subsides within 2 weeks during continued treatment. A low starting dose is advised to reduce the likelihood of this effect.
- The oral suspension contains parabens, sunset yellow, and sorbitol, which may cause allergic reactions in susceptible patients.
- There is an increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs. The mechanism is unknown.
- Avoid abrupt withdrawal as symptoms such as agitation, anxiety, dizziness, nausea, sleep disturbance (e.g. insomnia, intense dreams), and tremor can occur. Although generally mild, they can be severe in some patients. Withdrawal symptoms usually occur within the first few days of discontinuing treatment and they usually resolve within 2 weeks, though they can persist in some patients for up to 3 months or longer. See Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- The taper phase regimen used in clinical trials involved decreasing the daily dose by 10mg at weekly intervals.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

- *Very common*: nausea; sexual dysfunction (which may not be reversible after discontinuation).
- *Common*: abnormal dreams (including nightmares); agitation; appetite reduced; asthenia; anxiety; blurred vision; constipation; diarrhoea; dizziness; drowsiness; dry mouth (may be more common than with other SSRIs); headache; hyperlipidaemia; impaired concentration; insomnia; somnolence; sweating; tremor; vomiting; weakness; weight gain; yawning.
- *Uncommon*: abnormal bleeding (e.g. bruising); agitation; altered glycaemic control (in diabetics); confusion; extrapyramidal symptoms; hallucinations; mydriasis; nausea; postural hypotension; pruritus; rash; sinus tachycardia; transient increases or decreases in BP; urinary incontinence; urinary retention.
- *Rare*: abnormal LFTs; akathisia; arthralgia; anxiety (mainly during initial treatment); bradycardia; convulsions; depersonalization; hyponatraemia;

hypoprolactinaemia; manic reactions; menstrual disorders; myalgia; panic attacks; restless legs syndrome; seizures.
- *Very rare*: acute glaucoma; anaphylaxis; angioedema; GI bleeding; hepatic events (e.g. hepatitis); peripheral oedema; photosensitivity; priapism; serotonin syndrome; SIADH; Stevens–Johnson syndrome; thrombocytopenia; urticaria.
- *Unknown*: aggression; suicidal behaviour; suicidal ideation; tinnitus.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Paroxetine is a potent CYP2D6 inhibitor; it is also a substrate of CYP2D6 and inhibits its own metabolism to a certain degree. Minor metabolic pathways involve CYP3A4 and CYP1A2, which may become more important in patients with impaired CYP2D6 activity (e.g. long-term use of paroxetine, poor metabolizer status). Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Be mindful of CYP2D6 inhibition when switching antidepressants (see ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74).
- *Codeine*—reduced analgesic benefit.
- *Haloperidol*—increased risk of adverse effects from both drugs due to inhibition of CYP2D6. The clinical significance of co-administration with other inhibitors of CYP2D6 (see ➔ *Inhibitors* on the inside back cover) is unknown, but plasma concentrations of paroxetine may increase. The prescriber should be aware of the potential for interactions and that dose adjustments may be necessary.
- *Risperidone*—metabolism inhibited by paroxetine; increased risk of adverse effects.
- *Tamoxifen*—avoid combination, due to possible reduced efficacy of tamoxifen.
- *Tramadol*—reduced analgesic benefit.
- Drugs that affect gastric pH (e.g. PPIs, H_2 antagonists, antacids) can reduce the absorption of the oral suspension. Dose increases may be necessary if swapping from the tablet formulation.

Pharmacodynamic

- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 549)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *tapentadol*, *TCAs*, *tramadol*, and *trazodone*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.

- *Antidiabetics*—SSRIs may alter glycaemic control; risk of impaired awareness of hypoglycaemia.
- *Carbamazepine*—increased risk of hyponatraemia.
- *Cyproheptadine*—may inhibit the effects of paroxetine.
- *Diuretics*—increased risk of hyponatraemia.
- *Lithium*—may enhance the effect of SSRIs.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of anticholinergic effects and seizures (and serotonin toxicity).
- *NSAIDs*—increased risk of GI bleeding (potentially worse with aspirin and naproxen).
- *SNRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

It is recommended that doses are taken with or after food.

Anxiety/depression

- Initial dose 20mg PO OM, increased gradually up to a maximum of 50mg PO OM in 10mg increments, according to the patient's response.

Panic

- Initial dose 10mg PO OM, increased to a usual maximum of 40mg PO OM in 10mg increments, according to the patient's response. Further dose increases up to 60mg PO OM may be required.

+Pruritus

- Initial dose 5mg PO OM, increased to a maximum of 20mg PO OM. Doses of up to 40mg PO OM have been suggested. Any beneficial effect may be short-lived.

Dose adjustments

Elderly

- Normal initial doses can be used, but the maximum dose should not exceed 40mg PO daily.

Hepatic/renal impairment

- Increased plasma concentrations of paroxetine occur in patients with hepatic impairment or those with severe renal impairment (CrCl <30mL/min). Wherever possible, doses at the lower end of the range should be used. Patients may be more susceptible to adverse effects; for example, SSRIs can increase the risk of GI bleeding from varices.

Additional information

- Paroxetine tablets can be crushed and dispersed in water immediately prior to administration. The resulting solution may taste bitter or unpleasant and can have a local anaesthetic effect.
- Up to 10% of the Caucasian population are classified as CYP2D6 poor metabolizers, which will have implications for treatment.

- If withdrawal symptoms emerge during discontinuation, increase the dose to prevent symptoms and then start withdrawal more slowly.
- Withdrawal symptoms may be more common with paroxetine than with other SSRIs.
- Symptoms of anxiety or panic may worsen on initial therapy. This can be minimized by using lower starting doses.

Pharmacology

Paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake, with only very weak effects on noradrenaline and dopamine neuronal reuptake. Unlike other SSRIs, paroxetine binds to muscarinic M_3 receptors found in the brain, salivary glands, and smooth muscle. It has little affinity for α_1, α_2, D_2, 5-HT_1, 5-HT_2, and H_1 receptors. Paroxetine is metabolized primarily by CYP2D6 to virtually inactive metabolites, which are excreted by the kidneys; it is a potent inhibitor of CYP2D6 and a moderate inhibitor of CYP2B6.

References

1. Patel T, Yosipovitch G. Therapy of pruritus. *Expert Opin Pharmacother*. 2010;**11**(10):1673–82.
2. Aboukarr A, Giudice M. Interaction between monoamine oxidase B inhibitors and selective serotonin reuptake inhibitors. *Can J Hosp Pharm*. 2018;**71**(3):196–207.

Phenobarphital ⚠

Generic (CD3 POM)
Tablet: 15mg (28); 30mg (28); 60mg (28).
Elixir: 15mg/5mL (*some products contain alcohol*).
Injection (as phenobarbital sodium): 15mg/mL (10); 30mg/mL (10); 60mg/mL (10); 200mg/mL (10).

Indications

- Epilepsy (not absence seizures).
- +Status epilepticus.[1]
- +Terminal agitation (in patients who have failed to be controlled by usual interventions).[2]

Contraindications and cautions

- Phenobarbital is contraindicated in the following circumstances (however, for end-of-life care, while the prescriber must consider these conditions, they should not necessarily be a deterrent to use, providing the dose is carefully titrated):
  - acute intermittent porphyria
  - severe respiratory depression
  - severe hepatic/renal impairment.
- Use with caution in:
  - elderly
  - hepatic impairment (avoid if severe)
  - hypothyroidism (increased metabolism of levothyroxine)
  - renal impairment (avoid if severe)
  - respiratory depression (avoid if severe).
- Patients should be monitored for signs of suicidal ideation since anti-epileptic drugs have been associated with this behaviour.
- Avoid sudden withdrawal as a severe withdrawal syndrome may be precipitated (e.g. anxiety, delirium, dizziness, nausea, rebound insomnia, seizures, tremor).
- Life-threatening skin reactions (e.g. Stevens–Johnson syndrome, toxic epidermal necrolysis) have been reported with the use of phenobarbital. Patients should be advised of the signs and symptoms, and monitored closely for skin reactions. The greatest risk of occurrence is within the first weeks of treatment. If such a reaction occurs, phenobarbital must be withdrawn and never reintroduced.
- Phenobarbital may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Phenobarbital sodium injection is strongly alkaline and *must* be diluted in ten times its own volume with a suitable diluent (e.g. WFI or NaCl) before administration via IV injection. If necessary, it can be given *undiluted* by *deep* IM injection. It has been reported that phenobarbital via CSCI can be administered at a rate of 3mL/hr in concentrations no greater than 130mg/mL.[3]
- Although *not* contraindicated (see ➔ *Dose*, p. 556), administration of SUBCUT bolus injections should be avoided because tissue necrosis may

develop due to high pH. Nonetheless, a recent study concluded that SUBCUT injections at concentrations of 65mg/mL are well tolerated.[3] There was no correlation between the likelihood of injection site reaction and dosage strength or concentration of phenobarbital administered.

- Phenobarbital sodium injection contains propylene glycol 90% v/v, which, in high doses, may cause CNS adverse effects (e.g. drowsiness, confusion), haemolytic reactions, hepatic and renal toxicity, increase in plasma osmolarity, and lactic acidosis. The SmPC states the maximum daily licensed dose contains 177.9mg of propylene glycol.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- ataxia; cholestasis; confusion; delirium; drowsiness; hepatitis; hyperkinesia and behavioural disturbances in children; hypotension; lethargy; local necrosis following SUBCUT injection (avoid); megaloblastic anaemia (due to folate deficiency); memory and cognitive impairment (especially in the elderly); nystagmus; osteomalacia (with long-term treatment); paradoxical excitement/restlessness; respiratory depression (high doses).

Drug interactions

Pharmacokinetic

- Phenobarbital is metabolized by CYP2C19. It is also an inducer of CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP3A4, and UGT enzymes. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Affects many drugs through enzyme induction. Refer to ➔ *Inducers* on the inside back cover for a potential list of affected drugs, although the clinical significance is unknown. A selection of potential/actual interactions are shown below:
  - *alfentanil*—risk of reduced analgesic benefit
  - *celecoxib*—effect of celecoxib may be reduced; metabolism of phenobarbital may be reduced
  - *clonazepam*—effect of clonazepam may be reduced
  - *codeine*—possible altered analgesic effect (due to CYP3A4/UGT induction)
  - *corticosteroids*— reduced effect of corticosteroids; higher doses necessary (possibly double or more)
  - *escitalopram*—*may* increase exposure to phenobarbital
  - *haloperidol*—reduced effect of haloperidol
  - *fentanyl*—risk of reduced analgesic benefit
  - *fluconazole*—risk of increased exposure to phenobarbital
  - *levothyroxine*—increased metabolism may precipitate hypothyroidism
  - *midazolam*—effect of midazolam may be reduced
  - *mirtazapine*—effect of mirtazapine may be reduced

- *MAOIs*—may increase exposure to phenobarbital
- *modafinil*—effect of modafinil may be reduced; may enhance effect of phenobarbital
- *naloxegol*—effect of naloxegol will markedly decrease
- *oxycodone*—possible risk of reduced analgesic benefit
- *paracetamol*—may increase the risk of hepatoxicity of paracetamol
- *tramadol*—reduced analgesic benefit.

Pharmacodynamic

- *Antipsychotics*—seizure threshold lowered.
- *Antidepressants*—seizure threshold lowered.
- *CNS depressants*—risk of excessive sedation.
- *Nefopam*—increased risk of seizures.
- *Tapentadol*—increased risk of seizures.
- *Tramadol*—seizure threshold lowered.

Dose

NB—the parenteral formulation contains propylene glycol 90% v/v. See *Contraindications and cautions*, p. 554.

Epilepsy

- 60mg to 180mg PO ON.
- 50mg to 200mg as a single dose by IM or SUBCUT (although licensed, not recommended), or after 1 in 10 dilution with WFI, by IV injection, repeated if necessary after 6 hours.
- †Alternatively, 200mg to 400mg via CSCI over 24 hours (use a 30mL syringe and dilute maximally with NaCl or WFI). If necessary, give a stat dose of 100mg by IV injection (ensure dilution in ten times own volume, i.e. dilute 0.5mL with 5mL WFI) or deep IM injection (undiluted). The dose may be increased, if necessary, under specialist supervision.

†*Status epilepticus*

- Check local policies.
- Usually recommended as a third-line option after lorazepam and levetiracetam/phenytoin/sodium valproate.
- 10mg/kg by IV injection at a rate of no more than 100mg/min. Ensure dilution in ten times own volume with WFI.
- Subsequent treatment should be guided by local practice.

†*Terminal agitation*

- Initial dose 100mg to 200mg IM (undiluted) or IV (diluted with ten times own volume) injection. Continue treatment with 200mg to 600mg via CSCI over 24 hours (use a 30mL syringe and dilute maximally with NaCl or WFI). Higher doses may be used under specialist advice (up to 3400mg via CSCI have been reported).[4]

Dose adjustments

Elderly

- No specific dose adjustments are suggested. Use the lowest dose possible and monitor the patient closely since the elderly are more susceptible to adverse effects.

Hepatic/renal impairment

- Phenobarbital is contraindicated for use in severe hepatic or renal impairment. In mild to moderate impairment, no guidance is available; use the lowest effective dose and monitor for adverse effects.

Additional information

- Phenobarbital sodium injection has an extremely high osmolality, and maximum dilution in 30mL with either WFI or NaCl is recommended. The injection is alkaline (pH >9) and incompatible with most drugs via CSCI. Unless compatibility information is available, it should be administered via a separate CSCI.
- Therapeutic plasma concentration range (epilepsy): 15mg/L to 40mg/L or 65micromol/L to 170micromol/L.

Pharmacology

Phenobarbital is a sedative anti-epileptic which acts on $GABA_A$ receptors, increasing synaptic inhibition by modulation of chloride currents through receptor channels. It may also affect calcium channels.

It is readily absorbed from the GI tract, with a reported oral bioavailability approaching 100%. The rate of absorption is increased when formulated as a liquid, or if taken on an empty stomach, or when alcohol is ingested concurrently. Onset of action is approximately 1 to 2 hours following ingestion. Onset of action after IV injection occurs approximately 5 minutes after administration. Onset of action following SUBCUT injection is likely to be slightly faster than oral administration, but not as immediate as IV injection.

It is extensively hepatically metabolized, principally by CYP2C19 and it is a potent inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and UGT enzymes. Metabolism is affected by age, hepatic impairment, and concurrent medication (see Drug interactions, p. 555). One study suggests cancer patients, particularly cachectic and approaching end of life, may have reduced capacity to eliminate phenobarbital.[5] Approximately 25% of a dose is excreted unchanged in urine. Phenobarbital has a half life ranging from 80 to 120 hours.

References

1. Glauser T, Shinnar S, Gloss D, *et al*. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;**16**(1):48–61.
2. Stirling LC, Kurowska A, Tookman A. The use of phenobarbitone in the management of agitation and seizures at the end of life. *J Pain Symptom Manage*. 1999;**17**(5):363–8.
3. Hosgood JR, Kimbrel JM, McCrate Protus B, Grauer PA. Evaluation of subcutaneous phenobarbital administration in hospice patients. *Am J Hosp Palliat Care*. 2016;**33**(3):209–13.
4. Gillon S, Johnson M, Campbell C. Review of phenobarbitone use for deep terminal sedation in a UK hospice. *Palliat Med*. 2010;**24**(1):100–1.
5. Nakayama H, Echizen H, Ogawa R, Orii T, Kato T. Reduced clearance of phenobarbital in advanced cancer patients near the end of Life. *Eur J Drug Metab Pharmacokinet*. 2019;**44**(1):77–82.

Phenytoin

Epanutin® (POM)

The following preparations contain phenytoin sodium (see ➔ Additional information, p. 561).

Capsule: 25mg (28); 50mg (28); 100mg (84); 300mg (28).
Injection: 250mg/5mL (10).

Generic (POM)

Capsule: 25mg (28); 50mg (28); 100mg (84); 300mg (28).
Tablet: 100mg (28).
Injection: 250mg/5mL (5; 10).

The following products contain phenytoin base (see ➔ *Additional information*, p. 561).

Epanutin® (POM)

Chewable tablet (*Infatab®–scored*): 50mg (200).
Suspension: 30mg/5 mL (500mL).

Indications

- Generalized tonic–clonic and partial seizures.
- Trigeminal neuralgia (although carbamazepine preferred).
- Status epilepticus (*injection*).

Contraindications and cautions

- Use with caution in:
  - elderly (see ➔ *Dose adjustments*, p. 560)
  - Han Chinese and Thai populations (patients should be screened for HLA-B*1502 before initiating treatment, due to association with risk of developing Stevens–Johnson syndrome)
  - liver impairment (see ➔ *Dose adjustments*, p. 560)
  - porphyria.
- Patients should be monitored for signs of suicidal ideation since anti-epileptic drugs have been associated with this behaviour.
- Avoid abrupt withdrawal, unless clearly indicated, as seizures may be precipitated.
- Phenytoin can cause rare, serious skin adverse events. Ensure patients and/or their carers can recognize signs of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and advise they seek immediate medical attention if symptoms develop.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Phenytoin can affect bone mineral metabolism. Consider vitamin D supplementation in patients on long-term treatment and at risk of developing complications, e.g. immobilized patients, low dietary intake of calcium.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- ataxia; blood dyscrasias (including megaloblastic anaemia, thrombocytopenia, and aplastic anaemia); confusion; drowsiness; dysgeusia; gingival hyperplasia; headaches; hepatitis (discontinue immediately); hirsutism; hypersensitivity reactions*; hypertrichosis; insomnia; myoclonus/tremor; nausea; nystagmus; osteomalacia; paraesthesia; rash (morbilliform most common); slurred speech; Stevens–Johnson syndrome; thrombocytopenia; toxic epidermal necrolysis; vertigo; vomiting.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Phenytoin is a substrate primarily of CYP2C9 and CY2C19. It is also a strong inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and UGT enzymes. It is also extensively bound to serum plasma proteins and susceptible to competitive displacement. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition— see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index. Phenytoin may lower the plasma concentration, and diminish or even abolish the activity, of many drugs through enzyme induction.
- *Alfentanil*—risk of reduced analgesic benefit.
- *Apixaban*—effect of apixaban may be reduced.
- *Buprenorphine*—risk of reduced analgesic benefit.
- *Cannabidiol*—effect of cannabidiol may be reduced.
- *Celecoxib*—effect of celecoxib may be reduced.
- *Clonazepam*—effect of clonazepam may be reduced.
- *Codeine*—possible altered analgesic effect (due to CYP3A4/UGT induction).
- *Dexamethasone*—effect of dexamethasone likely to be reduced—dose doubling may be necessary; phenytoin plasma concentrations may also be affected (increased or decreased).
- *Diazepam*—interaction unpredictable (increase, decrease, and no effect have been reported).
- *Edoxaban*—effect of edoxaban may be reduced.
- *Fentanyl*—risk of reduced analgesic benefit.

* A delayed hypersensitivity disorder, known as hypersensitivity syndrome (HSS) or drug reaction with eosinophilia and systemic symptoms (DRESS), may occur within the first 3 months of treatment, although it may develop later. Symptoms include abnormal LFTs, arthralgia, fever, hepatitis, rashes, and vasculitis. It usually presents with initial symptoms which may resemble an acute viral infection. Acute anaphylactic shock has been reported. If such reactions do occur, phenytoin should be withdrawn immediately and permanently.

- *Fluconazole*—increases the plasma concentrations of phenytoin; consider alternative treatment or closely monitor phenytoin plasma concentration.
- *Fluoxetine*—risk of phenytoin toxicity.
- *Furosemide*—effect of furosemide may be reduced.
- *Haloperidol*—effect of haloperidol may be reduced.
- *Levothyroxine*—increased metabolism may precipitate hypothyroidism.
- *Metoclopramide*—theoretical risk of neurotoxicity due to possible increased rate of absorption of carbamazepine.
- *Midazolam*—effect of midazolam may be reduced.
- *Miconazole*—increases the plasma concentrations of phenytoin; consider alternative treatment or closely monitor phenytoin plasma concentration.
- *Mirtazapine*—effect of mirtazapine may be reduced.
- *Modafinil*—effect of modafinil may be reduced.
- *Naloxegol*—effect of naloxegol may be reduced.
- *Omeprazole*—risk of phenytoin toxicity with large doses of omeprazole (>40mg/day).
- *Oxycodone*—risk of reduced analgesic benefit.
- *Paracetamol*—may increase the risk of hepatoxicity of paracetamol.
- *Rivaroxaban*—effect of rivaroxaban may be reduced.
- *Sertraline*—risk of phenytoin toxicity.
- *Tramadol*—risk of reduced analgesic effect.
- *Trazodone*—risk of phenytoin toxicity (mechanism unknown).

Pharmacodynamic

- *Antipsychotics*—seizure threshold lowered.
- *Antidepressants*—seizure threshold lowered.
- *CNS depressants*—risk of excessive sedation.
- *Tramadol*—seizure threshold lowered.

Dose

Epilepsy

- Initial dose 150mg to 300mg (3mg/kg to 4mg/kg) PO daily as a single dose or in two divided doses. The dose can be increased gradually, with plasma concentrations being closely monitored. Usual maximum dose 500mg PO daily, although higher doses may be necessary (according to plasma concentrations).

Status epilepticus

- Check local policies.
- Give 10mg/kg to 15mg/kg (suggested maximum dose of 2000mg) at 50mg/min via IV injection into a large vein through a large-gauge needle or IV catheter. Give undiluted, and monitor ECG and BP.
- Some guidelines suggest a higher dose of 20mg/kg.
- Reduce the rate of injection to 25mg/min in the elderly or patients with cardiac disease.
- Subsequent treatment should be guided by local practice.
- Serum levels should be checked 24 hours post-loading dose.

Dose adjustments

Elderly

- Dose can be titrated to effect as per usual adult doses above.

Hepatic/renal impairment

- Lower doses may be necessary in patients with hepatic impairment since phenytoin is highly protein-bound and undergoes extensive hepatic metabolism. Adjust according to plasma concentration.
- Dose adjustments are unlikely to be required in patients with renal impairment. Although uraemia may affect protein binding, for any given dose, the free fraction of phenytoin is unlikely to change, such that patients may respond at lower-than-expected plasma concentrations.

Additional information

- Note that 100mg phenytoin sodium is equivalent to 92mg phenytoin, although these values are not necessarily biologically equivalent. In situations where it is necessary to change from one formulation to another, plasma concentration monitoring is advised.
- Therapeutic plasma concentration range: 10mg/L to 20mg/L (40micromol/L to 80micromol/L). Plasma samples are taken immediately prior to the next dose (at steady state). Plasma levels may need adjusting for low albumin if the laboratory reports total albumin.

Pharmacology

Phenytoin is an anti-epileptic drug that is believed to stabilize the seizure threshold by interfering with Na^+ and Ca^{2+} transport across cell membranes and to enhance GABA-mediated inhibition. After oral administration, it is well absorbed and highly protein-bound. It is metabolized by CYP2C9 and CY2C19, but this metabolism is saturable at concentrations that can occur clinically, hence the need for monitoring of plasma concentrations. It is a potent inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, and UGT enzymes. Many drugs are affected (see *Drug interactions*, p. 559).

Pramipexole

Standard-release

Mirapexin® (POM)

Tablet: 88 micrograms (30); 180 micrograms (*scored*—30; 100); 350 micrograms (*scored*—30; 100); 700 micrograms (*scored*—30; 100).

Generic (POM)

Tablet: 88 micrograms (30); 180 micrograms (30; 100); 350 micrograms (30; 100); 700 micrograms (30; 100).

Modified-release

Mirapexin® (POM)

Tablet: 0.26mg (30); 0.52mg (30); 1.05mg (30); 1.57mg (30); 2.1mg (30); 2.62mg (30); 3.15mg (30).

Generic (POM)

Tablet: 0.26mg (30); 0.52mg (30); 1.05mg (30); 1.57mg (30); 2.1mg (30); 2.62mg (30); 3.15mg (30).

Indications

- Parkinson's disease.
- Restless legs syndrome (up to 540 micrograms daily) (only standard-release formulations).

Contraindications and cautions

- Use with caution in patients with:
  - psychotic disorders (antagonism between drugs)
  - renal impairment
  - severe CV disease (risk of hypotension—monitor BP during initiation).
- Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep.
- Behavioural symptoms of impulse control disorders and compulsions, such as binge eating and compulsive shopping, can occur. Dose reduction/tapered discontinuation should be considered.
- Due to the risk of visual disturbances, ophthalmological monitoring is recommended at regular intervals.
- Pramipexole must not be suddenly discontinued due to the risk of NMS. This only applies to Parkinson's disease, as the dose for restless legs syndrome does not exceed 0.54mg daily (although rebound symptoms can develop). The recommended withdrawal schedule is as follows.
- Standard-release:
  - taper the dose at a rate of 0.54mg daily until the dose has been reduced to 0.54mg
  - reduce the dose thereafter by 0.264mg/day.
- Modified-release:
  - taper the dose at a rate of 0.52mg daily until the daily dose has been reduced to 0.52mg
  - reduce the dose thereafter by 0.26mg/day.

- Pramipexole may modify reactions and patients should be advised not to drive (or operate machinery) if affected.

Adverse effects

Adverse effects are generally dose-related. As such, they are more likely to be experienced by patients receiving pramipexole for Parkinson's disease than for restless legs syndrome.

- *Very common*: dizziness; drowsiness; dyskinesia; somnolence; nausea.
- *Common*: abnormal dreams; amnesia; behavioural symptoms of impulse control disorders; blurred vision; confusion; constipation; decreased appetite; fatigue; hallucinations; headache; hypotension; insomnia; peripheral oedema; restlessness; vomiting; visual disturbance; weight decrease.
- *Uncommon*: binge eating; cardiac failure; compulsive shopping; delusion; delirium; dyspnoea; hiccups; hyperkinesia; hyperphagia; hypersensitivity; hypersexuality; inappropriate ADH secretion; libido disorder; paranoia; pathological gambling; pneumonia; pruritus; rash; restlessness; sudden onset of sleep; syncope; weight increase.
- *Rare*: mania.
- *Unknown*: dopamine agonist withdrawal syndrome.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Pramipexole is mainly eliminated unchanged by the kidneys.
- Drugs that are secreted by the cationic transport system (e.g. *diltiazem*, *quinine*, *ranitidine*, *verapamil*) have the potential to interact with pramipexole, increasing plasma concentrations. The clinical significance is unknown and until further information is available, the following is suggested:
  - if pramipexole is co-administered with these drugs, slow and cautious titration is advisable
  - if these drugs are prescribed for a patient already using pramipexole, it is advisable to review the pramipexole dose (lower doses may be required).
- Drugs which affect renal function have the potential to interact with pramipexole. If such drugs are co-administered, regular monitoring of renal function is advisable. Such drugs include:
  - ACE-Is
  - NSAIDs.

Pharmacodynamic

- *Alcohol*—additive sedative effect.
- *CNS depressants*—additive sedative effect.
- *Dopamine antagonists (e.g. antipsychotics, metoclopramide)*—may decrease the efficiency of pramipexole due to dopamine antagonism.

Dose

Parkinson's-disease

Standard-release

- Initial dose 88 micrograms PO TDS. The dose can be doubled every 5–7 days if necessary and tolerated to 350 micrograms PO TDS.
- The dose can be further increased, if necessary, by 180 micrograms PO TDS at weekly intervals to a maximum of 3.3mg daily in three divided doses (i.e. 3 × 350 micrograms TDS).

Modified-release

- Initial dose 0.26mg PO OD. The dose can be doubled every 5–7 days if necessary and tolerated to 1.05mg PO OD. If a further dose increase is necessary, the daily dose should be increased by 0.52mg at weekly intervals up to a maximum dose of 3.15mg PO OD.

Restless legs syndrome

- Initial dose 88 micrograms PO 2–3 hours before bedtime.
- The dose can be doubled every 4–7 days, if necessary, to 350 micrograms PO daily.
- The dose can be further increased after 4–7 days to a maximum of 540 micrograms PO daily.

Dose adjustments

Elderly

- No specific guidance available. Dose requirements should be individually titrated.

Hepatic/renal impairment

- Dose adjustment in patients with hepatic impairment is not required.
- The elimination of pramipexole is dependent on renal function. The manufacturer gives advice on dosing that is dependent on the condition being treated.

Parkinson's disease

- Patients with CrCl >50mL/min require no reduction in dose.

Standard-release

- For CrCl 20 to 50mL/min, initial dose should be 88 micrograms PO BD. A maximum daily dose of 1.57mg PO OD should not be exceeded.
- If CrCl <20mL/min, the recommended dose is 88 micrograms PO OD. A maximum daily dose of 1.1mg PO OD should not be exceeded.
- If renal function deteriorates during treatment, reduce the dose by the same percentage as the decline in CrCl.

Modified-release

- For CrCl 30 to 50mL/min, initial dose 0.26mg PO ALT DIE, increasing to 0.26mg PO OD after 7 days. If necessary, the dose may be further increased by 0.26mg at weekly intervals up to a maximum dose of 1.57mg PO OD.

- For CrCl <30mL/min, treatment with modified-release tablets is not recommended and use of the standard-release formulation should be considered.

For restless legs syndrome

- Patients with CrCl >20mL/min require no reduction in dose.
- For patients with CrCl <20mL/min, a dose reduction will be necessary, although the initial dose cannot practically be reduced.

Additional information

- Pramipexole is given PO as the dihydrochloride monohydrate (DHCM) salt, but doses are described in terms of the base. Dose equivalents are shown below:
  - pramipexole base 88 micrograms = pramipexole DHCM 125 micrograms
  - pramipexole base 180 micrograms = pramipexole DHCM 350 micrograms
  - pramipexole base 350 micrograms = pramipexole DHCM 500 micrograms
  - pramipexole base 700 micrograms = pramipexole DHCM 1mg.
- Tablets can be crushed and mixed with water immediately prior to administration if necessary.

Pharmacology

Pramipexole is a dopamine agonist that binds with high selectivity and specificity to dopamine receptors, of which it has a preferential affinity for D_3 receptors. The mechanism of action of pramipexole as treatment for Parkinson's disease or restless legs syndrome is unknown, although in the former case, it is believed to be related to its ability to stimulate dopamine receptors in the striatum. Pramipexole is completely absorbed after oral administration. It is metabolized to a small extent, with most of the dose being renally excreted.

Prednisolone

Generic (POM)
Oral solution (unit dose): 5mg/5mL (10).
Oral solution: 10mg/mL (30mL).
Tablet: 1mg (28); 2.5mg (28; 30); 5mg (28; 30); 10mg (28; 30); 20mg (28; 30); 25mg (56); 30mg (28).
Tablet (gastro-resistant): 1mg (30); 2.5mg (28; 30); 5mg (28; 30).
Soluble tablet: 5mg (30).

Indications

- Suppression of inflammatory and allergic disorders.
- Also inflammatory bowel disease, asthma, immunosuppression, rheumatic disease, and adjunct to chemotherapy.
- Hypercalcaemia (associated with granulomatous causes, e.g. lymphoma, sarcoidosis).
- $^{+}$Appetite stimulation.

Contraindications and cautions

- In general, contraindications are relative in conditions where the use of prednisolone may be lifesaving.
- The use of prednisolone is contraindicated in systemic infection, unless specific anti-infective therapy is employed.
- Patients without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster.
- The MHRA has warned that corticosteroids carry a rare risk of central serous chorioretinopathy, with both local and systemic therapy. Patients should be advised to report any blurred vision or visual disturbances.
- Prednisolone may prevent the development of signs and symptoms of inflammation/infection (e.g. fever).
- Caution is advised when considering the use of systemic corticosteroids in patients with the following conditions:
  - concurrent use of NSAIDs (see ➔ *Drug interactions*, p. 568)
  - congestive heart failure
  - diabetes mellitus (risk of hyperglycaemia—close monitoring of blood glucose recommended)
  - epilepsy (see ➔ *Drug interactions*, p. 568)
  - glaucoma
  - hypertension
  - hypokalaemia (correct before starting prednisolone)
  - liver or renal impairment (see ➔ *Dose adjustments*, p. 569)
  - osteoporosis (see *BNF* for bisphosphonate guidance)
  - peptic ulceration
  - psychotic illness (symptoms can emerge within a few days or weeks of starting the treatment).
- In the presence of significant illness, trauma, or surgery, patients who have taken prednisolone at doses of >7.5mg PO OD, or stopped treatment within the past 3 months, may need additional corticosteroid treatment to compensate for a reduced adrenocortical response (e.g. IV hydrocortisone).

Prednisolone withdrawal

In patients who have received more than physiological doses of systemic corticosteroids (i.e. >7.5mg prednisolone) for >3 weeks, withdrawal should be gradual to avoid acute adrenal insufficiency. The speed of withdrawal should be determined on an individual basis. Abrupt withdrawal is unlikely to lead to clinically relevant hypothalamic–pituitary–adrenal axis suppression.

Consider gradual withdrawal for patients with the following:

- doses of systemic corticosteroid >40mg PO OD of prednisolone for >1 week
- received regular night-time doses
- received >3 weeks' treatment
- repeated courses of systemic steroids (especially if >3 weeks)
- short course within 1 year of stopping long-term treatment
- other causes of adrenal suppression.

Systemic corticosteroids may be stopped abruptly in patients whose disease is unlikely to relapse *and* have received treatment for ≤3 weeks *and* are not included in the groups above.

There is no evidence as to the best way to withdraw corticosteroids and it is often performed with close monitoring of the patient's condition. The dose may initially be reduced rapidly (e.g. by halving the dose daily) to physiological doses (equivalent to prednisolone 7.5mg PO OD), and then more slowly.

A 'withdrawal syndrome' may also occur, including fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules, and loss of weight.

In patients approaching the end of life, once the decision is made to withdraw corticosteroids, they can be discontinued abruptly. Patients with brain tumours may require additional analgesia, as raised intracranial pressure can develop and may manifest as worsening headache or terminal restlessness. If necessary, treatment can be continued via the SUBCUT route.

Adverse effects

The frequency is not defined. Adverse effects are generally predictable and related to dosage, timing of administration, and duration of treatment. Refer to the SmPC for a full list of adverse effects. They include:

- endocrine:
  - hirsutism; hyperglycaemia; hyperlipidaemia; weight gain
- fluid and electrolyte disturbances:
  - congestive heart failure; hypertension; hypokalaemia; Na^+ and water retention
- GI:
  - acute pancreatitis; dyspepsia and peptic ulceration with perforation; haemorrhage; hiccups (if problematic, may resolve if alternative corticosteroid used)

- musculoskeletal:
  - aseptic necrosis of the femoral head; avascular necrosis; loss of muscle mass; osteoporosis; myopathy (can present within 2 weeks of high-dose treatment); tendon rupture
- neurological:
  - aggravation of epilepsy; anxiety; confusion; depression; insomnia; mood elevation; psychotic reactions (management of corticosteroid-induced psychiatric reactions involves dose reduction or discontinuation)
- other:
  - glaucoma; impaired wound healing; increased susceptibility and severity of infections (signs can be masked); sweating.

Corticosteroid-induced osteoporosis

- Patients aged over 65 years and with prior or current exposure to oral corticosteroids are at increased risk of osteoporosis and bone fracture. Treatment with corticosteroids for periods as short as 3 months may result in increased risk. Three or more courses of corticosteroids taken in the previous 12 months are considered to be equivalent to at least 3 months of continuous treatment.
- Prophylactic treatment (e.g. bisphosphonate, calcium and vitamin D supplements, hormone replacement therapy) should be considered for all patients who may take an oral corticosteroid for 3 months or longer.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Prednisolone is a substrate of CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Note that low activity of CYP3A4 (e.g. through inhibition) can contribute to the development of osteonecrosis of the femoral head.
- *Carbamazepine*—effect of prednisolone likely to be reduced; consider doubling the prednisolone dose and monitor the response.
- *Colestyramine*—may decrease the absorption of prednisolone.
- *Clarithromycin/erythromycin*—may increase the effects of prednisolone through inhibition of CYP3A4.
- *Phenytoin*—effect of prednisolone likely to be reduced; consider doubling the prednisolone dose and monitor the response.
- Avoid excessive amounts of grapefruit juice, as it may increase the bioavailability of prednisolone through inhibition of intestinal CYP3A4.

Pharmacodynamic

- *Anticoagulants*—increased risk of bleeding.
- *Antihypertensives*—effect antagonized by prednisolone.

- *Ciclosporin*—additive immunosuppressive effect; convulsions reported with combination.
- *Diuretics*—effect antagonized by prednisolone; increased risk of hypokalaemia and hyperglycaemia.
- *Hypoglycaemic drugs*—effect antagonized by prednisolone.
- *NSAIDs*—increased risk of GI toxicity.
- *SSRIs*—increased risk of bleeding.

Dose

- Refer to the SmPC for specific conditions.
- Initial doses range from 10mg to 20mg PO OD (severe disease—up to 60mg PO daily) preferably in the morning.
- With acute conditions, the dose can usually be reduced after a few days but also may need to be continued for several weeks or months, tapering to the lowest effective dose.
- Maintenance dose usually between 2.5mg and 15mg PO OD.

Hypercalcaemia

- Initial dose 20mg to 40mg PO OM for up to 5 days.
- Subsequent doses should be guided by biochemistry, but long-term treatment (e.g. 10mg PO OD) may be required.

†*Appetite*

- Initial dose 15mg to 40mg PO OM. Dose reduction should be guided by symptom response.

Dose adjustments

Elderly

- No specific dose adjustments are necessary. Use the lowest dose for the shortest duration possible since the elderly are more susceptible to adverse effects.

Hepatic/renal impairment

- No specific guidance available. The lowest effective dose should be used for the shortest duration possible.

Additional information

- Prednisolone is less commonly used in palliative care than dexamethasone, as it has a slightly higher mineralocorticoid activity.
- Consider oral hygiene with prednisolone use. The patient may develop oral thrush and may need a course of nystatin.
- Oral anti-inflammatory corticosteroid equivalences are:
  - dexamethasone 750 micrograms = hydrocortisone 20mg = prednisolone 5mg.

Pharmacology

Prednisolone is a synthetic corticosteroid used as a replacement or adjunctive therapy in a wide range of inflammatory or allergic conditions. It is rapidly and almost completely absorbed after oral administration. Prednisolone is metabolized primarily in the liver by CYP3A4 to inactive metabolites which, together with small amounts of unchanged drug, are excreted renally.

Pregabalin ♡

Lyrica® (CD3 POM)
Capsule: 25mg (56; 84); 50mg (84); 75mg (56); 100mg (84); 150mg (56); 200mg (84); 225mg (56); 300mg (56).
Oral solution: 20mg/mL (473mL).

Generic (CD3 POM)
Capsule: 25mg (56; 84); 50mg (56, 84); 75mg (14, 56); 100mg (56, 84); 150mg (56); 200mg (56, 84); 225mg (56); 300mg (56).
Tablets: 25mg (56); 50mg (84); 75mg (56); 100mg (84); 150mg (56); 200mg (84); 225mg (56); 300mg (56).
Oral solution: 20mg/mL (473mL).

Indications

- Central and peripheral neuropathic pain.
- Generalized anxiety disorder.
- Adjunctive therapy for partial seizures.
- [+]Restless legs syndrome.[(1)]
- [+]Sleep improvement.[(2)]
- [+]Sweats.[(3)]
- [+]Uraemic pruritus.[(4)]

Contraindications and cautions

- Pregabalin has been associated with a rare risk of respiratory depression. The following factors may increase the risk of this adverse effect:
  - compromised respiratory function
  - respiratory or neurological disease
  - renal impairment
  - use of concomitant CNS depressants (e.g. benzodiazepines, opioids—see below)
  - elderly.
- Pregabalin (at doses >300mg/day), in combination with an opioid, has been infrequently associated with dose-dependent respiratory depression, coma, and death.[(5)] This may be explained by opioid-induced GI hypomotility and a possible increase in pregabalin absorption. Additionally, pregabalin may attenuate opioid tolerance, with consequential development of opioid adverse effects such as sedation and respiratory effects. For this reason, slower titration (than the licensed dose schedule) is recommended when pregabalin is added for a patient already receiving an opioid.
- Adverse effects, such as dizziness, drowsiness, and, in some cases, loss of consciousness, have been reported during initial treatment. Patients should be advised of these potential effects and to exercise caution until they are familiar with how the drug affects them.
- Although not mentioned by *CredibleMeds®*, there is a possible risk of QT prolongation/TdP (the SmPC states a rare adverse effect):
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 572)

  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- Use with caution in patients with:
  - congestive heart failure (usually elderly CV-compromised patients)
  - diabetes mellitus (may need to adjust hypoglycaemic treatment as weight gain occurs)
  - elderly (see ➔ *Dose adjustments*, p. 573)
  - renal impairment (see ➔ *Dose adjustments*, p. 573).
- Avoid sudden withdrawal. Discontinue gradually over at least 1 week in order to avoid adverse effects such as nausea, vomiting, dizziness, hyperhidrosis, flu syndrome, anxiety, and insomnia. These withdrawal effects have been reported even after short-term use. In epileptic patients, abrupt withdrawal of anti-epileptics can precipitate status epilepticus, although there is no evidence of rebound seizures with pregabalin.
- Suicidal ideation and behaviour have been reported with anti-epileptics.
- Pregabalin is associated with visual disturbances such as blurred vision or other changes of visual acuity. Discontinuation of pregabalin may lead to resolution or improvement of symptoms.
- If affected by visual disturbances, drowsiness, and dizziness, patients should be warned about driving. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: dizziness; drowsiness; headache.
- *Common*: abdominal distension; amnesia; increased appetite; arthralgia; ataxia; back pain; cognitive disorder; confusion; constipation; abnormal coordination; diarrhoea; dry mouth; dysarthria; euphoria; flatulence; abnormal gait; irritability; muscle cramp; nasopharyngitis; nausea; nystagmus; peripheral oedema; sexual dysfunction (erectile dysfunction; reduced libido); speech disorder; tremor; visual disturbance (blurred vision; diplopia); vomiting; increased weight (effect may plateau after 3–4 months).
- *Uncommon*: ageusia; aggression; agitation; anorexia; apathy; asthenia; atrioventricular block; bradycardia; chest tightness; congestive heart failure; cough; depersonalization; depression; abnormal dreams; dyskinesia; dyspnoea; dysuria; epistaxis; facial oedema; gastro-oesophageal reflux disease; hallucination; hot flushes; hyperacusis; hyperaesthesia; hyperglycaemia; hyperhidrosis; hypersensitivity; hypertension; oral hypoaesthesia; hypoglycaemia; hyporeflexia; hypotension; elevated liver enzymes; loss of consciousness; malaise; myalgia; myoclonus; nasal congestion; nasal dryness; neutropenia; nystagmus; panic attack; pruritus; psychomotor hyperactivity; pyrexia; rash; restlessness; rhinitis; salivary hypersecretion; sexual dysfunction (anorgasmia, breast pain, dysmenorrhoea, delayed ejaculation, increased libido); snoring; stupor; syncope; tachycardia; thirst; urinary

incontinence; visual disturbance (asthenopia; dry eye; eye pain; eye swelling; increased lacrimation; peripheral vision loss; photopsia; reduced visual acuity; visual field defect); weight loss.
- *Rare*: angioedema; disinhibition; dysgraphia; dysphagia; hypokinesia; oscillopsia; pancreatitis; parosmia; pulmonary oedema; QT prolongation; renal failure; rhabdomyolysis; sexual dysfunction (amenorrhoea, breast discharge, breast enlargement, gynaecomastia); Stevens–Johnson syndrome; visual disturbance (keratitis, mydriasis, strabismus, visual brightness).
- *Unknown*: respiratory depression.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- No clinically significant pharmacokinetic drug interactions.

Pharmacodynamic
- Pregabalin carries a *small* risk of prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 570).
- *Opioids* and *CNS depressants*—possible opioid-sparing affect, necessitating opioid dose review; increased risk of CNS adverse effects and risk of respiratory depression).

Dose

All formulations of pregabalin are priced equally. Avoid using multiple capsules to fulfil a dose. Pregabalin is licensed for both BD and TDS dosing. There may be reasons for selecting a TDS regime, but prescribers are encouraged to use BD dosing initially.

Pain
- The licensed schedule is shown in Table 3.17. This may be poorly tolerated by elderly patients or those with cancer, and for these patients, a more cautious titration is suggested. Whichever strategy is adopted, adverse effects are more common at around the time of dose escalation but usually resolve in a few weeks. Slower titration may be preferred in the elderly or cancer populations, although it may take longer to appreciate the therapeutic benefit.

Epilepsy
- Initial dose 75mg PO BD, increased if necessary to 150mg PO BD after 7 days. The dose can be increased further to a maximum of 300mg PO BD after an additional 7 days. Dose titration may need to be individualized if poorly tolerated.

Table 3.17 Licensed and suggested dose schedules for pregabalin

Licensed dose		Suggested dose	
Day 1	75mg PO BD	Day 1	25mg PO ON
Days 3–7	150mg PO BD	Day 2	25mg PO BD
Days 10–14	300mg PO BD	Days 6–7	75mg PO BD
Increase dose according to response. Maximum dose of 600mg daily		Increase dose by 25mg BD every 2 days, as needed, to a maximum of 600mg daily	

Anxiety

- Initial dose 75mg PO BD, increased as necessary after 7 days in steps of 150mg daily, to a maximum of 300mg PO BD.
- A more cautious approach may be warranted in patients taking opioids or other CNS depressants.

†Sleep/†restless legs syndrome

- Usual initial dose 150mg PO ON, increased by 150mg at weekly intervals to a dose of 450mg PO ON. For restless legs syndrome, if daytime symptoms are still present at this point, an additional 75mg to 150mg PO OD (e.g. 2 p.m.) can be taken.
- A more cautious approach may be warranted in patients taking opioids or other CNS depressants (e.g. initial dose of 50mg PO ON).

†Chronic pruritus/†sweats

- Titrate the dose as shown in Table 3.17 (suggested dose) to a usual maximum of 150mg PO BD.

Dose adjustments

Elderly

- May require a more cautious titration, as described in Table 3.17 (suggested dose), or may need a dose reduction due to renal impairment (see Table 3.18).

Hepatic/renal impairment

- No dose adjustment is required for patients with hepatic impairment.
- Dose adjustments are necessary for patients in renal failure or undergoing haemodialysis, as shown in Table 3.18. Adjust the starting dose as necessary.

Table 3.18 Dose adjustments of pregabalin according to renal impairment

Creatinine clearance (mL/min)	Maximum daily dose
≥60	300mg PO BD
≥30 to <60	150mg PO BD
≥15 to <30	75mg PO BD or 150mg PO OD
<15	75mg PO OD

- A supplementary dose should be given immediately following every 4-hour haemodialysis treatment.

Additional information

- Pregabalin is exempt from the safe custody arrangements, under the Misuse of Drugs (Safe Custody) Regulations 1973. Prescription requirements are, however, necessary.
- Neuropathic pain and anxiety can improve within a week.
- Pregabalin readily dissolves in water. If necessary, the capsules may be opened and mixed with water prior to use. The solution may have a bitter taste; there are no problems flushing the solution down an enteral feeding tube.
- Several studies reviewing conversion of gabapentin to pregabalin predict that a rough ratio for conversion is about 6:1 gabapentin to pregabalin.[5]

Pharmacology

Pregabalin is an anti-epileptic which reduces the release of neurotransmitters through interaction with the $\alpha_2\delta$ subunit of voltage-dependent Ca^{2+} channels. Its bioavailability is >90%, which, unlike gabapentin, is independent of dose. Pregabalin is excreted by the kidneys, with 98% of an administered dose being excreted unchanged in the urine, so dose adjustment is required in renal impairment (see *Dose adjustments*, p. 573).

References

1. Garcia-Borreguero D, Larrosa O, Williams AM, *et al*. Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study. *Neurology*. 2010;**74**(23):1897–904.
2. Manas A, Ciria JP, Fernandez MC, *et al*. Post hoc analysis of pregabalin vs. non-pregabalin treatment in patients with cancer-related neuropathic pain: better pain relief, sleep and physical health. *Clin Transl Oncol*. 2011;**13**(9):656–63.
3. Loprinzi CL, Qin R, Balcueva EP, *et al*. Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. *J Clin Oncol*. 2010;**28**(4):641–7.
4. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol*. 2016;**75**(3):619–25.e6.
5. Gomes T, Greaves S, van den Brink W, *et al*. Pregabalin and the risk for opioid-related death: a nested case-control study. *Ann Intern Med*. 2018;**169**(10):732–4.
   Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010;**49**(10):661–9.

Pridinol

Generic (POM)
Tablet: 3mg (20; 100) See ➔ *Additional information*.

Indications

- Treatment of central and peripheral muscle spasms.

Contraindications and cautions

- Contraindicated for use in patients with:
  - arrhythmia
  - GI obstruction
  - glaucoma
  - prostate hypertrophy
  - syndrome with urinary retention.
- Pridinol should be used with caution in the following situations:
  - elderly (see ➔ *Dose adjustments*, p. 576)
  - hypotension
  - severe hepatic and/or renal impairment (see ➔ *Dose adjustments*, p. 576).

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Uncommon*: abdominal pain; asthenia; dizziness; dry mouth; fatigue; headache; hypotension (see ➔ *Dose*); nausea; restlessness; tachycardia.
- *Rare*: anxiety; attention disorder; depression; diarrhoea; hypersensitivity (dyspnoea, mucosal oedema, pruritus); taste disorder; visual impairment (accommodation); vomiting.

Drug interactions

Pharmacokinetic

- Pridinol is metabolized primarily via CYP2C19 and CYP2B6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Anticholinergics*—increased risk of adverse effects.
- *Antihypertensives*—possible increased risk of hypotension.
- *Domperidone*—may inhibit the prokinetic effect.
- *Metoclopramide*—may inhibit the prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.

Dose

- 1.5mg to 3mg PO TDS.
- The duration of administration is decided by the prescriber.

- Patients who suffer from hypotension should take the tablets after meals to reduce the risk of fainting.

Dose adjustments

Elderly

- No specific dose reductions are recommended in the SmPC. However, it is suggested that elderly patients are initiated on the lower end of the usual range. Elderly patients are particularly susceptible to adverse anticholinergic effects.

Hepatic/renal impairment

- There are no specific instructions for dose reduction in hepatic impairment. It is contraindicated for use in *severe* hepatic impairment and should be used with caution in patients with mild to moderate hepatic impairment. If the drug must be used, the patient should be closely monitored and the lowest effective dose should be prescribed.
- There are no specific instructions for dose reduction in renal impairment. It is contraindicated for use in *severe* renal impairment and should be used with caution in patients with mild to moderate renal impairment. Pridinol is largely excreted via the kidneys within 24 hours, partly in unchanged form and partly as conjugates. If the drug must be used, the patient should be closely monitored and the lowest effective dose should be prescribed.

Additional information

- At the time of writing (November 2022), *Myopridin*® is about to be withdrawn from the UK market. An unlicensed product is available to import.
- The onset of action is faster if pridinol is taken before meals.
- Tablets can be crushed and dispersed in water or orange juice immediately prior to administration. The resulting solution is suitable for administration via a feeding tube.

Pharmacology

Pridinol is a centrally acting muscle relaxant that reduces polysynaptic reflexes via an anticholinergic action. It acts on both smooth and striated muscles. This effect is used for the treatment of skeletal muscle tension of both central and peripheral origin. Maximum plasma concentration occurs within 1 hour after oral administration, with the onset of action occurring faster if taken before meals. Metabolism is via CYP2C19 and CYP2B6, and pridinol is renally eliminated as a combination of unchanged drug and conjugates. A broad range of elimination half-lives have been reported (8.97–34.85 hours). This interpatient variability may be explained partly by the prevalence of CYP polymorphisms, particularly CYP2C19 poor metabolizers.[1]

Reference

1. Richter M, Donath F, Wedemeyer RS, Warnke A, Horstmann A, Peschel C. Pharmacokinetics of oral pridinol: results of a randomized, crossover bioequivalence trial in healthy subjects. *Int J Clin Pharmacol Ther*. 2021;**59**(6):471–7.

Prochlorperazine ♡

Stemetil® (POM)
Tablet: 5mg (28, 84).
Syrup: 5mg/5mL (100mL).
Injection: 12.5mg/mL (*not for SUBCUT use*).

Generic (POM)
Buccal tablet: 3mg (8, 50).
Tablet: 5mg (28, 84).
NB—prochlorperazine 3mg buccal tablets can be sold OTC for the relief of nausea and vomiting associated with migraines in adults over 18 years (P).

Buccastem M® (P)
Tablet (buccal): 3mg (8).

Generic (P)
Tablet (buccal): 3mg (8).

Indications

- Anxiety.
- Nausea and vomiting.
- Schizophrenia/psychosis.

Contraindications and cautions

- Avoid use in patients with:
  - agranulocytosis
  - cardiac failure
  - dementia (unless the patient is at immediate risk of harm or severely distressed; increased mortality reported)
  - hepatic dysfunction (see ➔ *Dose adjustments*, p. 579)
  - hypothyroidism
  - myasthenia gravis
  - narrow-angle glaucoma
  - Parkinson's disease
  - phaeochromocytoma
  - prostate hypertrophy
  - renal dysfunction (see ➔ *Dose adjustments*, p. 579).
- Antipsychotic drugs may increase the risk of VTE; assess risks before and during treatment.
- Use with caution in:
  - diabetes mellitus (hyperglycaemia or intolerance to glucose has been reported)
  - elderly—risk of hyperthermia and hypothermia in hot and cold weather, respectively; risk of postural hypotension (see ➔ *Dose adjustments*, p. 579)
  - epilepsy (lowers seizure threshold).
- The SmPC states there is a *potential** risk of QT prolongation/TdP.

* Currently not mentioned in the *CredibleMeds®* database.

  - Avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*).
  - Avoid concomitant administration of drugs that impair elimination (see ➔ *Drug interactions*).
  - Avoid in patients with known QT interval prolongation or congenital long QT syndrome.
  - Electrolyte disturbances must be corrected (e.g. hypokalaemia) before initiation.
- Warn the patient about:
  - the importance of reporting signs of infection such as sore throat and fever during initial treatment (risk of agranulocytosis)
  - reducing exposure to direct sunlight (or ultraviolet lamps) due to the risk of photosensitization (usually with higher doses).
- Prochlorperazine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- agitation; akathisia (restlessness; may occur with antiemetic doses); blurred vision; constipation; dry mouth; galactorrhoea; gynaecomastia; impotence; insomnia; NMS; Parkinsonian symptoms; postural hypotension; tardive dyskinesia (involuntary movements of the face, jaw, or tongue; may be irreversible, even after withdrawal); thermoregulation problems (hyper- or hypothermia); urinary retention; visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Prochlorperazine is believed to be metabolized by CYP2C19, CYP2D6, and CYP3A4.
- Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary.

Pharmacodynamic

- Prochlorperazine can cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Anticholinergics*—increased risk of adverse effects.
- *Anti-epileptics*—dose may need to be increased to take account of the lowered seizure threshold.
- *Antihypertensives*—increased risk of hypotension.
- *CNS depressants*—additive sedative effect.
- *Haloperidol*—may be an additive hypotensive effect; increased risk of extrapyramidal symptoms.
- *Levodopa and dopamine agonists*—effect antagonized by prochlorperazine.
- *Metoclopramide*—increased risk of extrapyramidal symptoms.
- *Opioids*—may be an additive hypotensive effect.
- *Trazodone*—may be an additive hypotensive effect.

Dose

Anxiety

- Initial dose 15mg to 20mg PO daily in divided doses (e.g. 5mg TDS or 10mg BD). Increase to a maximum of 40mg PO daily in divided doses.

Nausea and vomiting

- 5mg to 10mg PO BD or TDS. Alternatively, 12.5mg by deep IM injection, followed by oral medication 6 hours later, if necessary.
- *Buccastem*®: 3mg to 6mg BD, placed in the buccal cavity.

Psychosis

- Initial dose 12.5mg PO BD for 7 days, increasing as necessary by 12.5mg PO daily at 4- to 7-day intervals. Usual effective daily dosage is 75mg to 100mg (in divided doses). After some weeks at the effective dosage, an attempt should be made at dose reduction. Daily doses of 25mg to 50mg have been shown to be effective.

Dose adjustments

Elderly

- A lower initial dose is recommended due to the increased susceptibility to adverse effects, particularly postural hypotension and drug-induced Parkinsonism after prolonged use.

Hepatic/renal impairment

- The manufacturer advises prochlorperazine should be avoided in patients with hepatic and/or renal dysfunction. Nonetheless, if prochlorperazine must be prescribed, lower doses should be used. Patients may be more susceptible to adverse effects due to accumulation of the drug and/or metabolite(s).

Additional information

- Prochlorperazine injection must not be administered SUBCUT.

Pharmacology

Prochlorperazine is a piperazine phenothiazine drug related to chlorpromazine. The mechanism of action of prochlorperazine has not been fully

determined, but its antiemetic effect is believed to be mainly due to D_2 antagonism. However, it also displays some acetylcholine and H_1 receptor antagonism, although in the latter case, it appears to occur on chronic dosing. Prochlorperazine also blocks α_1-adrenoceptors. It has a low and variable bioavailability due to extensive first-pass metabolism. It is believed to be metabolized by several cytochromes, including CYP2C19, CYP2D6, and CYP3A4.

Promethazine ⚠ ♡

Phenergan® (P)
Tablet: 10mg (56); 25mg (56).
Oral solution: 5mg/5mL (100mL).

Phenergan® (POM)
Injection: 25mg/mL (10).

Sominex® (P)
Tablet: 20mg (8; 16).

Generic (P)
Tablet: 10mg (56); 25mg (56).

Indications

- Symptomatic treatment for allergic conditions.
- Treatment of insomnia.
- Nausea and vomiting (including by $CSCI^{+}$).

Contraindications and cautions

- Contraindicated for use in patients with CNS depression.
- The SmPC states that promethazine should be avoided in patients taking MAOIs up to 14 days previously.
- There is a *possible* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 582)
  - avoid concomitant administration of drugs that impair elimination (see ➔ *Drug interactions*, p. 582)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- There is a potential risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when promethazine is used concomitantly with certain serotonergic drugs. Treatment should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Promethazine should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 582).
- Promethazine should be used with caution in patients with:
  - asthma or other respiratory disorders, e.g. bronchitis or bronchiectasis (may thicken or dry lung secretions and impair expectoration)
  - diabetes (may rarely affect glycaemic control)
  - epilepsy (may reduce the seizure threshold)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 583)
  - narrow-angle glaucoma
  - prostatic hypertrophy
  - pyloroduodenal obstruction

  - renal impairment (see ➔ *Dose adjustments*, p. 583)
  - severe congestive heart failure
  - severe coronary artery disease
  - urinary retention.
- Avoid direct strong sunlight as photosensitivity reactions have been reported.
- Promethazine is not generally recommended for SUBCUT administration because of the risk of local necrosis.[1] However, when diluted in an adequate amount of NaCl, it can usually be administered over 24 hours via CSCI without significant problems.[2]
- The anticholinergic effect of promethazine can be additive with other drugs. Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Promethazine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- arrhythmia; blood dycrasias (rare); blurred vision; confusion; disorientation; dizziness; drowsiness; dry mouth; extrapyramidal effects (less common); headaches; hypersensitivity reactions (rare); hypotension; jaundice (rare); nasal congestion; nightmares; photosensitive skin reactions; rash; restlessness; seizures; tiredness; urinary retention.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Promethazine is metabolized by CYP2D6 (major) and CYP2B6; *in vitro* data suggest it may be moderate CYP2D6 inhibitor. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Anticholinergics*—increased risk of adverse effects.
- *Antidiabetics*—glycaemic control may be rarely impaired.
- *Antihypertensives*—increased risk of hypotension.
- *CNS depressants*—increased risk of CNS adverse effects.
- *Domperidone*—may inhibit the prokinetic effect.

- *MAOIs*—avoid concurrent administration of MAOIs (including *linezolid*, *moclobemide*, *rasagiline*, and *selegiline)* or within 2 weeks of discontinuation of their use (*NB—initial low doses, careful titration, and close monitoring may permit safe combination*).
- *Metoclopramide*—may inhibit the prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *Opioids*—increased risk of hypotension.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

Although it is rapidly absorbed after oral administration, substantial first-pass metabolism reduces absolute bioavailability to around 25%. When converting from oral to parenteral administration, a dose reduction of at least 50% should take place.

Symptomatic treatment for allergic conditions

- 10mg to 20mg PO BD to TDS.
- Alternatively, 25mg to 50mg deep IM (maximum 100mg/day).

Treatment of insomnia

- 20mg to 50mg PO ON.

Nausea and vomiting

- Usual dose 25mg PO 6- to 8-hourly.
- Lower doses may be adequate: 10mg to 25mg PO 6- to 12-hourly.
- ⁺Alternatively, 6.25mg to 12.5mg via CSCI, diluted to a volume of at least 20mL with NaCl. Doses of up to 100mg daily have been suggested.[3]

NB—do not give by SUBCUT injection.

Dose adjustments

Elderly

- No specific guidance is available, although lower starting doses may be preferable. Dose requirements should be individually titrated. Note that the elderly may be more susceptible to the central and anticholinergic effects of cyclizine (which may be additive with concomitant drugs); there may be an increased risk of cognitive decline and dementia.

Hepatic/renal impairment

- For patients with hepatic or renal impairment, although no information exists, it is advisable to use low initial doses and titrate to effect.

Additional information

- Promethazine via CSCI is physically compatible under stated conditions with glycopyrronium.[4]
- There are conflicting reports of physical compatibility with dexamethasone and morphine sulfate, suggesting there may be concentration-dependent incompatibilities.[4]

Pharmacology

Promethazine is a phenothiazine which acts as an antagonist at H_1 and muscarinic receptors. It also displays moderate 5-HT_{2C} and D_2 receptor antagonism, with a lesser affinity for the 5-HT_{2A} receptor. Although it is rapidly

absorbed after oral administration, substantial first-pass metabolism reduces absolute bioavailability to around 25%; smaller parenteral doses should be adequate. Promethazine is cleared from the body mainly by hepatic metabolism, with <1% being excreted unchanged. Three metabolites have been identified: hydroxylated promethazine, monodesmethylpromethazine, and promethazine sulfoxide. The major metabolite is hydroxylated promethazine, which is produced via the interaction with CYP2D6; demethylation of promethazine is catalysed by CYP2B6.

References

1. Medicines and Healthcare products Regulatory Agency. Phenergan® injection. Summary of product characteristics. Available from: http://www.mhra.gov.uk/spc-pil/. Accessed 30 December 2019.
2. WA Cancer and Palliative Care Network. Evidence based clinical guidelines for adults in the terminal phase, 2nd Edition. Government of Western Australia, Department of Health. 2011. Available from: https://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Palliative/Evidence_based_guidelines.pdf. Accessed 30 December 2019.
3. Seidel R, Sanderson C, Mitchell G, Currow DC. Until the chemist opens—palliation from the doctor's bag. *Aust Fam Physician*. 2006;**35**(4):225–31.
4. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Propantheline

Pro-Banthine® (POM)
Tablet: 15mg (112).

Indications

- Smooth muscle spasm (e.g. bladder, bowel).
- Sweating.
- Urinary frequency.

Contraindications and cautions

- Propantheline is contraindicated in patients with:
  - hiatus hernia associated with reflux oesophagitis
  - myasthenia gravis
  - narrow-angle glaucoma
  - obstructive diseases of the GI or urinary tract
  - paralytic ileus
  - prostatic enlargement
  - pyloric stenosis
  - severe ulcerative colitis
  - toxic megacolon.
- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- It should be used with caution in the following:
  - autonomic neuropathy (such as those with Parkinson's disease)
  - cardiac disease (e.g. arrhythmia, congestive heart failure, coronary heart disease, hypertension—risk of tachycardia)
  - dementia
  - Down's syndrome
  - elderly (see ➔ *Dose adjustments*, p. 586)
  - GI reflux disease
  - hepatic impairment
  - hyperthyroidism (risk of tachycardia)
  - pyrexia (reduces sweating)
  - renal impairment
  - ulcerative colitis.
- Monitoring is recommended, especially in the first few months after initiating therapy or increasing the dose, due to the risk of CNS effects such as agitation, confusions, drowsiness, and hallucinations.
- Patients should be advised to seek advice if they develop sudden loss of visual acuity or ocular pain (risk of narrow-angle glaucoma).
- Regular dental check-ups are advisable during long-term treatment due to the risk of oral complications caused by reduced salivary secretions (e.g. dental caries, oral candidosis).
- Propantheline may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- confusion; difficulty with micturition; dizziness; drowsiness; dry mouth; inhibition of sweating; palpitations; tachycardia; visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Propantheline may reduce gastric emptying and therefore affect the absorption of concomitant drugs.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Donepezil*—effect may be antagonized.
- *β_2-agonists*—increased risk of tachycardia.
- *Cyclizine*—increased risk of anticholinergic adverse effects.
- *Domperidone*—may inhibit the prokinetic effect.
- *Galantamine*—effect may be antagonized.
- *Metoclopramide*—may inhibit the prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *Rivastigmine*—effect may be antagonized.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

Tablets should be taken at least 1 hour before food.

- Initial dose 15mg PO BD to TDS, increased if necessary up to a maximum of 30mg PO QDS.

Dose adjustments

Elderly

- No specific guidance available. Use the lowest effective dose, as the elderly may be more susceptible to adverse effects. In particular, there is an increased risk of cognitive decline and dementia.

Hepatic/renal impairment

- No specific guidance available. Use the lowest effective dose.

Additional information

- Tablets may be dispersed in water immediately prior to administration if necessary.

Pharmacology

Propantheline is a quaternary ammonium anticholinergic drug which blocks the action of acetylcholine at post-ganglionic sites, including smooth muscle, secretory glands, and CNS sites. It inhibits peristalsis, reduces gastric acid secretion, and also decreases pharyngeal, tracheal, and bronchial secretions. Propantheline is poorly absorbed from the bowel, partly due to the polar nature of the molecule and partly due to extensive first-pass metabolism in the small intestine prior to absorption.

Propranolol

Standard-release

Generic (POM)
Tablet: 10mg (28); 40mg (28); 80mg (56); 160mg (56).
Oral solution: 5mg/5mL (150mL); 10mg/5mL (150mL); 40mg/5mL (150mL); 50mg/5mL (150mL).

Modified-release

Half-Inderal LA® (POM)
Capsule: 80mg (28).
Inderal LA® (POM)
Capsule: 160mg (28).
A variety of other products are available and include Bedranol SR®, Beta Prograne®/Half Beta Prograne®, Slo-Pro®; consult the BNF for more information.

Indications

Propranolol has a variety of indications (refer to the SmPC for further details); those listed below reflect indications likely to be encountered in the palliative care setting:

- anxiety
- portal hypertension
- ⁺sweats.

Contraindications and cautions

- Contraindicated for use in:
  - asthma
  - bradycardia (HR <45–50 beats/min)
  - hypotension
  - metabolic acidosis
  - untreated phaeochromocytoma.
- Use with caution in patients with:
  - COPD
  - concurrent administration of diltiazem or verapamil (see ➔ *Drug interactions*, p. 588)
  - concurrent administration of other antihypertensive drugs (see ➔ *Drug interactions*, p. 588)
  - diabetes (can impair glucose tolerance)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 589)
  - low systolic BP (<90mmHg)
  - overt heart failure (may be used in patients whose signs of failure have been controlled)
  - renal impairment (see ➔ *Dose adjustments*, p. 589).
- Do not withdraw abruptly, especially in patients with ischaemic heart disease.
- Propranolol may increase the sensitivity to known allergens.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: bradycardia; breathlessness; cold extremities; fatigue; Raynaud's phenomenon; sleep disturbances (e.g. nightmares).
- *Uncommon*: diarrhoea; nausea; vomiting.
- *Rare*: alopecia; angioedema; bronchospasm; confusion; deterioration of heart failure; dizziness; dry eyes; exacerbation of intermittent claudication; hallucinations; memory loss; mood changes; paraesthesia; postural hypotension; precipitation of heart block; psychoses; purpura; rash; thrombocytopenia; visual disturbances.
- *Very rare*: dyslipidaemia; hypoglycaemia (particularly in the elderly and those on antidiabetic treatment).
- *Unknown*: agranulocytosis; arthralgia; conjunctivitis; constipation; depression; dry mouth; dyspnoea; headache; impotence; worsening angina pectoris.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Propranolol is primarily metabolized by CYP1A2 and CYP2D6, with direct glucuronidation also occurring via UGT1A9, UGT2B4, and UGT2B7. Concomitant use of drugs that are substrates of, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, one or more of these pathways may lead to clinically relevant drug interactions. Propranolol is also a substrate of P-gp, although the clinical relevance is unknown.
- Smoking induces the hepatic metabolism of propranolol; sudden cessation may lead to the development of adverse effects.

Pharmacodynamic

- *Antihypertensives*—increased risk of hypotension.
- *Clonidine*—propranolol may exacerbate rebound hypertension that can occur on withdrawal of clonidine; if both are co-administered, withdraw propranolol several days before discontinuing clonidine.
- *Digoxin*—increased risk of bradycardia.
- *Diltiazem*—increased risk of hypotension and atrioventricular block.
- *Haloperidol*—potential increased risk of hypotension.
- *Insulin/oral antidiabetic drugs*—symptoms of hypoglycaemia may be masked.
- *Levomepromazine*—potential increased risk of postural hypotension.
- *NSAIDs*—may reduce the hypotensive effect of bisoprolol.
- *Verapamil*—increased risk of hypotension and atrioventricular block.

Dose

Anxiety

Standard-release

- Initial dose 40mg PO OD, increased to 40mg PO TDS if necessary.

Modified-release

- Initial dose 80mg PO OD, increased to 160mg PO OD if necessary.

Portal hypertension

Standard-release

- Initial dose 40mg PO BD, increased to 80mg PO BD if necessary, depending on HR response. The dose can be increased incrementally to a maximum dose of 160mg PO BD.

Modified-release

- Initial dose 80mg PO OD, increased to 160mg PO OD if necessary, depending on HR response. The dose can be increased further in 80mg increments to a maximum dose of 320mg PO OD.

[+]Sweats

- There is little evidence to support the use of propranolol for sweating associated with cancer. Nonetheless, an initial dose of 10mg PO BD, increasing as tolerated to a maximum of 40mg PO TDS (as for anxiety), may be tried.

Dose adjustments

Elderly

- No specific guidance is available; use the lowest effective dose.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. Manufacturers advise caution, given the hepatic metabolism, and suggest patients with severe liver disease should be started on a lower initial dose (e.g. 10mg to 20mg PO OD) and titrate to the lowest effective dose. For this reason, modified-release formulations should only be used once the dose has been successfully titrated.
- No specific guidance is available for patients with renal impairment. Use lower initial doses and titrate according to response.

Pharmacology

Propranolol is a non-selective β-adrenergic receptor antagonist. It is also a weak antagonist of 5-HT_1 receptors. Propranolol is available as a racemic mixture of two enantiomers R(+) and S(−). Most of the pharmacological action is due to the S(−)-enantiomer. Propranolol is highly lipophilic and undergoes extensive first-pass metabolism in the liver via CYP1A2 and CYP2D6, as well as by direct glucuronidation; it is also a substrate of P-gp. Most metabolites are eliminated in the urine.

Quetiapine ♡

Standard-release

Seroquel® (POM)
Tablet: 25mg (60); 100mg (60); 200mg (60); 300mg (60).

Generic (POM)
Tablet: 25mg (60); 100mg (60); 150mg (60); 200mg (60); 300mg (60).
Oral suspension: 20mg/mL (150mL).

Modified-release

Seroquel® XL (POM)
Tablet: 50mg (60); 150mg (60); 200mg (60); 300mg (60); 400mg (60).

Generic (POM)
Tablet: 50mg (60); 150mg (60); 200mg (60); 300mg (60); 400mg (60).

Indications

- Schizophrenia.
- Bipolar disorder (manic/depressive episodes).
- Refractory depression (*modified-release*).
- ⁺Agitation associated with dementia.(1)
- ⁺Delirium.(2)

Contraindications and cautions

⚠ Warning
- Antipsychotic drugs have been associated with an elevated risk of VTE. Several potential mechanisms have been described, including drug-induced sedation, obesity, hyperprolactinaemia, increased platelet aggregation (by 5-HT_{2A} antagonism), and elevation of antiphospholipid antibody.
- Quetiapine should not be used to treat behavioural symptoms of dementia. Elderly patients with dementia-related psychosis treated with quetiapine are at increased risk of CVA and mortality.
- A risk of excess mortality has been consistently observed in elderly patients with dementia treated with antipsychotics. The mechanism of mortality may be CV in nature (e.g. arrhythmia susceptibility from QT prolongation or increased risk of VTE). Conventional antipsychotics (e.g. haloperidol) are likely to carry a greater risk of mortality than second-generation antipsychotics (e.g. quetiapine, risperidone).
- The risks associated with CVA (e.g. diabetes, hypertension, smoking) should be assessed before commencing treatment with quetiapine.

- Concomitant administration of cytochrome CYP3A4 inhibitors (e.g. clarithromycin, erythromycin) is contraindicated (see ➔ *Drug interactions*, p. 592).
- Avoid grapefruit juice, as it may increase the bioavailability of quetiapine through inhibition of intestinal CYP3A4.
- Quetiapine should be used with caution in the following circumstances:

  - CV disease (quetiapine may induce postural hypotension—see Drug interactions, p. 592 and Dose adjustments, p. 594)
  - cerebrovascular disease (risk of cerebrovascular events with antipsychotics)
  - diabetes mellitus (risk of hyperglycaemia and weight gain; rare reports of hypoglycaemia)
  - epilepsy (may lower the seizure threshold; the SmPC suggests low risk)
  - hepatic impairment (see Dose adjustments, p. 594)
  - history of drug-induced neutropenia (discontinue in patients with a neutrophil count $<1.0 \times 10^9$/L).
- Appropriate monitoring of weight, blood glucose, and lipids is advisable if treatment persists beyond 3 months to detect antipsychotic-induced changes. In addition, an increase in body weight may be a predisposing factor for the development or exacerbation of diabetes.
- Quetiapine is associated with a *conditional* risk of QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see Drug interactions, p. 592)
  - avoid concomitant administration of drugs that impair elimination (see Drug interactions, p. 592)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia) before commencing treatment.
- There is a risk of paradoxical serotonin toxicity (see Chapter 1, *Serotonin toxicity*, p. 29) when quetiapine is used concomitantly with certain drugs (quetiapine is a 5-HT_{2A} antagonist). Treatment should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Quetiapine should be used cautiously with other drugs that display serotonergic effects (see Drug interactions, p. 592).
- Concurrent use of adrenaline and antipsychotics may cause dose-dependent severe hypotension and tachycardia (the α-adrenergic antagonist effects of antipsychotics can result in decreased peripheral resistance and adrenaline may have significant β_2-adrenergic-mediated vasodilatory effects).
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Quetiapine has been associated with the development of akathisia, which is most likely to occur within the first few weeks of treatment. Review continued treatment as increasing the dose may be detrimental.
- If a patient develops signs and symptoms indicative of NMS, such as altered mental status, autonomic instability (e.g. cardiac dysrhythmia, diaphoresis), hyperpyrexia, and muscle rigidity, or presents with unexplained high fever without additional clinical manifestations of NMS, quetiapine must be discontinued.
- Elderly patients are more susceptible to adverse effects (see Dose adjustments, p. 594). Subtle deficits in attention, memory, and reasoning

may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Gradual withdrawal over a period of at least 1–2 weeks is recommended in order to avoid withdrawal symptoms such as diarrhoea, dizziness, headache, insomnia, irritability, nausea, and vomiting. The incidence of these symptoms significantly reduces after 7 days.
- Quetiapine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.
- *Very common*: dizziness; drowsiness (onset usually within the first 3 days of treatment); dry mouth; extrapyramidal symptoms (e.g. akathisia); lowered haemoglobin; headache; lipid metabolism affected (elevated LDL cholesterol and triglycerides; decreased HDL cholesterol); weight gain (at least >7% increase; occurs within the first few weeks of treatment); withdrawal symptoms (on discontinuation).
- *Common*: abnormal dreams (including nightmares); elevated ALT/GGT (asymptomatic); increased appetite; asthenia; blurred vision; constipation; dysarthria; dyspepsia; dyspnoea; hyperglycaemia; hyperprolactinaemia; irritability; leucopenia; palpitations; peripheral oedema; postural hypotension; pyrexia; suicidal ideation; syncope (especially during the initial dose titration period; α_1 antagonism); thyroid hormones affected (reduced T4—free and total—concentration; increased TSH); tachycardia; vomiting.
- *Uncommon*: anaemia; bradycardia; diabetes mellitus (and exacerbation of); dysphagia; AST elevated; hypersensitivity (including allergic skin reactions); hypoglycaemia (US SmPC); hyponatraemia; hypothyroidism (reduced T3 levels); neutropenia; QT prolongation; restless legs syndrome; rhinitis; seizure; sexual dysfunction; tardive dyskinesia; thrombocytopenia; urinary retention.
- *Rare*: agranulocytosis; galactorrhoea; hepatitis; hypothermia; ileus; jaundice; metabolic syndrome; menstrual disorder; NMS (see ➔ *Contraindications and cautions*, p. 590); pancreatitis; priapism; somnambulism; VTE.
- *Very rare*: anaphylaxis; SIADH; rhabdomyolysis; severe cutaneous adverse reactions (Stevens–Johnson syndrome, toxic epidermal necrolysis, and DRESS have been reported in association with quetiapine treatment).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Quetiapine is metabolized by CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or

inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, this pathway may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index. There is a risk of prolongation of the QT interval with co-administration of CYP3A4 inhibitors (see ➔ *Contraindications and cautions*, p. 590).

- *Carbamazepine*—decreases quetiapine plasma concentrations.
- *Clarithromycin*—potential to increase quetiapine plasma concentrations.
- *Erythromycin*—potential to increase quetiapine plasma concentrations.
- *Fluconazole*—potential to increase quetiapine plasma concentrations (although more likely to occur when fluconazole doses >200mg daily).
- *Grapefruit juice*—potential to increase quetiapine plasma concentrations.
- *Phenytoin*—decreases quetiapine plasma concentrations.
- *Rifampicin*—decreases quetiapine plasma concentrations.

Pharmacodynamic

- Quetiapine has been associated with prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Adrenaline*—α-adrenergic effects may be blocked, with consequential paradoxical hypotension and tachycardia.
- *Anticholinergics*—increased risk of adverse effects.
- *Antidiabetics*—impaired glycaemic control (risk of hyperglycaemia).
- *Antihypertensives*—increased risk of hypotension.
- *CNS depressants*—additive sedative effect.
- *Domperidone*—may reduce the prokinetic effect.
- *Haloperidol*—increased risk of extrapyramidal reactions.
- *Levodopa and dopamine agonists*—effect antagonized by quetiapine.
- *Levomepromazine*—increased risk of extrapyramidal reactions; additive hypotensive effect.
- *Metoclopramide*—increased risk of extrapyramidal reactions.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *Opioids*—may be an additive hypotensive effect.
- *SNRIs/SSRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—may be an additive hypotensive effect (and serotonin toxicity).

Dose

Standard-release

Schizophrenia

- Initial dose 25mg PO BD on day 1, then 50mg PO BD on day 2, then 100mg PO BD on day 3, and then 150mg PO BD on day 4. Further dose

adjustments should be titrated according to response, to a maximum dose of 375mg PO BD. Usual range is 150mg to 225mg PO BD.

Bipolar disorder (mania)

- Initial dose 50mg PO BD on day 1, then 100mg PO BD on day 2, then 150mg PO BD on day 3, and then 200mg PO BD on day 4. Further dose adjustments should be titrated according to response, to a maximum of 400mg PO BD. Daily dose increments should not be greater than 200mg. Once the acute episode has resolved, the lowest effective dose may be used for maintenance therapy.

Bipolar disorder (depression)

- Initial dose 50mg PO ON (day 1), then 100mg PO ON (day 2), then 200mg PO ON (day 3), and then 300mg PO ON (day 4). Further dose adjustments may be necessary in only a few patients; the maximum dose is 600mg PO ON. Once the acute episode has resolved, the lowest effective dose may be used for maintenance therapy.

[+]Agitation/delirium

- Suggested initial dose is 12.5mg to 25mg PO ON, increasing as necessary up to 50mg PO BD. Higher doses may be needed, but the risk of adverse effects will increase.

Modified-release

Schizophrenia

- Initial dose 300mg PO OD on day 1, then 600mg PO OD on day 2. Adjust dose according to response. Maximum dose is 800mg/day.

Bipolar disorder (mania)

- Initial dose 300mg PO OD on day 1, then 600mg PO OD on day 2. Adjust dose according to response. Maximum dose is 800mg/day.

Bipolar disorder (depression)

- Initial dose 50mg PO ON (day 1), then 100mg PO ON (day 2), then 200mg PO ON (day 3), and then 300mg PO ON (day 4). Further dose adjustments should be titrated according to response, to a maximum dose of 600mg PO ON; usual maintenance dose is 300mg PO ON.

Refractory depression (adjunctive treatment)

- 50mg PO ON for 2 days, then 150mg PO ON for 2 days. Further dose adjustments should be titrated according to response, to a maximum dose of 300mg PO ON.

Dose adjustments

Elderly

- Quetiapine can induce postural hypotension during initiation, more commonly in the elderly. A dose reduction and more gradual titration are recommended, should this occur. Refer to individual SmPCs for specific details. Note the lower starting dose suggested above for delirium[+] (see ➔ *Dose*).
- For refractory depression, the initial dose of *modified-release* formulations should be 50mg PO ON for 3 days, increasing if necessary to 100mg PO ON for at least 4 days, before further adjusting the dose

in 50mg increments every 4 days, according to response. Note that the usual maximum dose of 300mg PO ON should not be attained until at least day 22.
- For all other indications, *modified-release* formulations should be started at 50mg PO OD. The dose can be increased in increments of 50mg daily to an effective dose, depending on the clinical response.

Hepatic/renal impairment
- Use with caution in patients with hepatic impairment. An initial dose of 25mg PO daily is recommended by the manufacturer, with further daily increases in increments of 25mg to 50mg until an effective dose is attained.
- Dose adjustments are unnecessary in renal impairment.

Additional information
- *Standard-release* tablets can be halved.
- Patients taking divided doses of *standard-release* products can be switched to *modified-release* products at the equivalent total daily dose taken OD. Note that dose adjustment may be required.
- Of the antipsychotics, quetiapine is believed to have a low risk of extrapyramidal symptoms (clozapine also does, but it is rarely used due to the risk of haematological issues). Should delirium or agitation develop in a patient with Parkinson's disease, low-dose quetiapine may be considered in difficult cases (maximum 50mg to 75mg PO daily).

Pharmacology
Quetiapine is a second-generation antipsychotic agent. Quetiapine and the active metabolite norquetiapine act as antagonists at 5-$HT_{2A/2B/2C}$, 5-HT_7, and D_1/D_2 receptors. The higher selectivity for 5-HT_2, relative to dopamine D_2, receptors is believed to contribute to the antipsychotic effect, yet with a low risk of extrapyramidal symptoms, compared to typical antipsychotics.

Quetiapine and norquetiapine also act as high-affinity H_1 and α_1-receptor antagonists and moderate-affinity α_2 receptor antagonists. Norquetiapine has moderate to high affinity for muscarinic receptor subtypes M_1, M_3, and M_5, thus leading to anticholinergic adverse effects such as dry mouth and constipation.

The antidepressant effect of quetiapine is believed to be due to additional pharmacological activity of the metabolite norquetiapine. This acts as a noradrenaline reuptake inhibitor and as a partial agonist at 5-HT_{1A} receptors.

Quetiapine is well absorbed following oral administration, and extensively metabolized by CYP3A4 to the major metabolite norquetiapine (which is also extensively metabolized by CYP3A4). Less than 5% of a dose is excreted as unchanged drug.

References
1. Ringman JM, Schneider L. Treatment options for agitation in dementia. *Curr Treat Options Neurol*. 2019;**21**(7):30.
2. Hui D, Dev R, Bruera E. Neuroleptics in the management of delirium in patients with advanced cancer. *Curr Opin Support Palliat Care*. 2016;**10**(4):316–23.

Rabeprazole ♡

Pariet® (POM)

Tablet: 10mg (28); 20mg (28).

Generic (POM)

Tablet: 10mg (28); 20mg (28).

Indications

- Treatment of gastric and duodenal ulcers.
- Treatment of reflux oesophagitis.
- Symptomatic gastro-oesophageal reflux disease.
- [+]Treatment and prophylaxis of NSAID-associated benign gastric and duodenal ulcers requiring continual therapy.
- Eradication of *Helicobacter pylori* (*not discussed*).
- Zollinger–Ellison syndrome (*not discussed*).

Contraindications and cautions

- Increased gastric pH resulting from rabeprazole treatment may critically affect the absorption of certain drugs (see ➔ *Drug interactions*, p. 597).
- Treatment with rabeprazole may lead to a slightly increased risk of developing GI infections (e.g. *Clostridium difficile*). Therefore, avoid unnecessary use or high doses.
- Use with caution in patients with severe hepatic dysfunction (see ➔ *Dose adjustments*, p. 598).
- Rebound acid hypersecretion may occur on discontinuation if the patient has received >8 weeks' treatment.
- Rabeprazole is predominantly metabolized by CYP2C19, and CYP3A4 to a lesser extent. Factors affecting CYP2C19 activity, such as phenotype (see Box 1.3) and drugs (see ➔ *Drug interactions*, p. 597), can alter response and adverse effects.
- PPIs are associated with a range of electrolyte disturbances such as hyponatraemia and hypomagnesaemia (and associated hypocalcaemia and hypokalaemia). Suspect the PPI, should unexplainable symptoms present (e.g. confusion, delirium, generalized weakness, nausea). The effect on Na^+ metabolism is unclear, possibly involving ADH. PPIs may reduce active Mg^{2+} absorption in the small intestine by affecting function of a transient receptor protein channel.
- There is a *conditional* risk of QT prolongation/TdP due to the propensity to cause significant electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia). Monitor electrolytes regularly in patients with known QT interval prolongation or congenital long QT syndrome and in those taking drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 597).
- When used in high doses and over long durations (>1 year), PPIs may increase the risk of hip, wrist, and spine fracture, predominantly in the elderly or in the presence of other recognized risk factors. Consider the need for adequate vitamin D and calcium intake.
- Rabeprazole may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; asthenia; back pain; benign fundic gland polyps; constipation; cough; diarrhoea; dizziness; flatulence; headache; infection; influenza-like illness; insomnia; nausea; non-specific pain; pharyngitis; rhinitis; vomiting; weakness.
- *Uncommon*: abnormal LFTs; arthralgia; bronchitis; chest pain; chills; drowsiness; dyspepsia; dry mouth; eruction; erythema; fracture of the hip, spine, or wrist; leg cramps; myalgia; pyrexia; nervousness; rash; sinusitis; somnolence; urinary tract infections.
- *Rare*: anorexia; blood dyscrasias; bullous reactions; depression; gastritis; hepatic encephalopathy; hepatitis; hypersensitivity; interstitial nephritis; jaundice; pruritus; stomatitis; sweating; taste disturbance; visual disturbance; weight gain.
- *Very rare*: erythema multiforme; Stevens–Johnson syndrome; toxic epidermal necrolysis.
- *Unknown*: confusion; gynaecomastia; hypomagnesaemia; hyponatraemia; microscopic colitis; peripheral oedema.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Rabeprazole is metabolized by CYP2C19 and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Drugs with pH dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced
  - *ferrous sulfate*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g. 100mg) at the same as ferrous sulfate to improve absorption
  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations
  - *metronidazole suspension*—rabeprazole may reduce/prevent the absorption of metronidazole.
- *Antacids*—should be given at least 1 hour before rabeprazole (reduced bioavailability).
- *Fluconazole*—may cause increased pantoprazole concentrations (CYP2C19 inhibition).
- *Methotrexate*—rabeprazole may cause increases in levels of methotrexate; consider withholding rabeprazole.

Pharmacodynamic

- Rabeprazole may cause prolongation of the QT interval due to the propensity to cause electrolyte disturbances. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Corticosteroids*—concurrent use may increase the risk of osteoporosis and osteoporotic fractures.

Dose

Treatment of benign gastric and duodenal ulcers

- 20mg PO OM for 4–8 weeks.

Treatment of gastro-oesophageal reflux disease

- 20mg PO OM for 4–8 weeks.

Maintenance of gastro-oesophageal reflux disease

- 10mg to 20mg PO OM.

+Treatment and prophylaxis of NSAID-associated peptic ulcer disease

- 20mg PO OM for 8 weeks
- Maintenance 10mg to 20mg PO OM.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- No dose adjustments are necessary for patients with liver or renal impairment. However, the SmPC states use with caution in patients with severe liver impairment. Given the hepatic metabolism, using lower initial doses would be prudent.

Additional information

- Tablets should not be chewed or crushed but should be swallowed whole. Consider switching to another PPI if there is difficulty swallowing tablets or administration via an 8Fr nasogastric tube is required (e.g. lansoprazole).

Pharmacology

Rabeprazole is a gastric PPI, reducing the release of H^+ from parietal cells by inhibiting H^+/K^+ ATPase. It is rapidly inactivated by gastric acid; hence oral formulations are enteric-coated. It is extensively metabolized by CYP2C19 and CYP3A4, and the metabolites are excreted principally in the urine. Note that CYP2C19 poor metabolizers (or patients taking CYP2C19 inhibitors) can have significantly higher plasma concentrations, leading to unexpected results.

Ranitidine

All formulations of ranitidine are affected due to ongoing regulatory investigations into the presence of the contaminant N-nitrosodimethylamine (NDMA) in samples of ranitidine-active substance. At present, all suppliers of ranitidine in Europe have had their Certificate of Suitability (CEP) suspended. Therefore, until regulatory investigations are complete, no further supplies of ranitidine products can be manufactured (October 2022).

Zantac® (POM)
Syrup (sugar-free): 75mg/ 5mL (300mL).
Injection: 50mg/2mL (5).

Generic (POM)

Tablet: 150mg (60); 300mg (30).
Effervescent tablet: 150mg (60); 300mg (30).
Oral solution: 75mg/5mL (100mL; 300mL); 150mg/5mL (150mL).
Injection: 50mg/2mL (5).

NB—ranitidine can be sold for short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for prevention of these symptoms when associated with consumption of food or drink in those aged over 16 years, at a maximum single dose of 75mg and a maximum daily dose of 300mg.

Indications

- Treatment of duodenal and benign gastric ulcers.
- Prevention of NSAID-associated duodenal ulcers.
- Oesophageal reflux disease.
- Chronic episodic dyspepsia.
- Symptomatic relief in gastro-oesophageal reflux disease.
- Zollinger–Ellison syndrome.
- ✚Prevention of NSAID-associated gastric ulcers.

Contraindications and cautions

- Use with caution in patients with renal impairment (see *Dose adjustments*, p. 601).
- Ranitidine should be avoided in patients with a history of acute porphyria.
- The elderly may be at greater risk of developing community-acquired pneumonia when prescribed ranitidine.
- *Zantac®* effervescent tablets contain aspartame—avoid in phenylketonuria (check individual generic products).

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Uncommon*: abdominal pain; constipation; hypersensitivity reactions; nausea.
- *Rare*: abnormal LFTs; raised plasma creatinine; skin rash.
- *Very rare*: acute interstitial nephritis; acute pancreatitis; alopecia; anaphylactic shock; arthralgia; atrioventricular block; blood dyscrasias;

blurred vision (reversible); bradycardia; confusion; depression; diarrhoea; dizziness; dyskinesia; erythema multiforme; gynaecomastia; galactorrhoea; impotence (reversible); hallucinations; headache; hepatitis; jaundice; myalgia; tachycardia; vasculitis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- It is a minor substrate of CYP1A2, CYP2C19, and CYP2D6. It is unlikely to be involved in cytochrome-related interactions.
- Drugs with pH-dependent absorption can be affected:
  - *atazanavir*—avoid combination due to substantially reduced absorption
  - *digoxin*—increased plasma concentrations possible
  - *erlotinib*—avoid combination as bioavailability of erlotinib can be significantly reduced
  - *ferrous sulfate*—reduced absorption likely to result in treatment failure; some recommend co-administration of ascorbic acid (e.g. 100mg) at the same as ferrous sulfate to improve absorption
  - *ketoconazole/itraconazole*—risk of sub-therapeutic plasma concentrations
  - *metronidazole suspension*—ranitidine may reduce/prevent the absorption of metronidazole.

Pharmacodynamic

- No clinically significant interactions noted.

Dose

Treatment of duodenal and benign gastric ulcers

- 150mg PO BD or 300mg PO ON for at least 4 weeks
- A further 4-week course may be necessary; 8 weeks' treatment may be required for ulcers associated with NSAIDs.

Prevention of NSAID-associated gastric/duodenal ulcers

- 300mg PO BD
- [+]Alternatively, 100mg to 200mg via CSCI over 24 hours.

Oesophageal reflux disease

- 150mg PO BD or 300mg PO ON for 8–12 weeks
- Dose can be switched to 150mg PO QDS in severe cases
- [+]Alternatively, 100mg to 200mg via CSCI over 24 hours.

Chronic episodic dyspepsia

- 150mg PO BD for up to 6 weeks
- [+]Alternatively, 100mg to 200mg via CSCI over 24 hours.

Gastro-oesophageal reflux disease

- 150mg PO BD for 2 weeks
- [+]Alternatively, 100mg to 200mg via CSCI over 24 hours.

Zollinger–Ellison syndrome

- 150mg PO TDS, increased as necessary up to a maximum of 6g PO daily in divided doses.

Dose adjustments

Elderly

- No dose adjustments are necessary. However, given the risk of developing community-acquired pneumonia, ranitidine should be used at the lowest dose and for the shortest duration possible.

Hepatic/renal impairment

- For hepatic impairment, no specific guidance is available. However, ranitidine is excreted via the kidneys mainly as the free drug, so dose adjustments are unlikely.
- In patients with CrCl <50mL/min, the daily dose of ranitidine should be 150mg PO ON (or 100mg by $CSCI^{+}$). This can be increased to 150mg PO BD (or 200mg by $CSCI^{+}$), if necessary, and reviewed after 4–8 weeks.

Additional information

- Ranitidine is generally considered a second-line option as a gastro-protective agent; PPIs remain the first choice. However, in certain circumstances, such as intolerable adverse effects or metabolic disturbances, ranitidine may be preferred.
- Ranitidine is reportedly *chemically and physically* compatible under stated conditions in combination with morphine sulfate and dexamethasone sodium phosphate. Under stated conditions, ranitidine is *physically* compatible with furosemide, glycopyrronium, morphine hydrochloride, oxycodone, and tramadol. It is incompatible with levomepromazine, midazolam, and phenobarbital.[1]

Pharmacology

Ranitidine is a non-imidazole histamine H_2 receptor antagonist that blocks the action of histamine on parietal cells in the stomach, thereby decreasing gastric acid secretion.

Reference

1. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Risperidone ⚠ ♡

Risperdal® (POM)

Tablet (scored): 500 micrograms (20); 1mg (20, 60); 2mg (60); 3mg (60); 4mg (60); 6mg (28).
Liquid: 1mg/mL (100mL).

Generic (POM)

Tablet (scored): 500 micrograms (20); 1mg (20, 60); 2mg (60); 3mg (60); 4mg (60); 6mg (28, 60).
Liquid: 1mg/mL (100mL).
Orodispersible tablet: 500 micrograms (28); 1mg (28); 2mg (28), 3mg (28); 4mg (28).

Indications

- Psychosis.
- Short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia (with risk of harm).
- †Delirium.(1)
- †Antiemetic (refractory nausea and vomiting).(2)
- †Major depression.(3)

Contraindications and cautions

⚠ Warning

- Antipsychotic drugs have been associated with an elevated risk of VTE. Several potential mechanisms have been described, including drug-induced sedation, obesity, hyperprolactinaemia, increased platelet aggregation (by 5-HT_{2A} antagonism), and elevation of antiphospholipid antibody.
- Risperidone should not be used to treat behavioural symptoms of dementia. Elderly patients with dementia-related psychosis treated with risperidone are at increased risk of CVA and mortality. Citalopram, sertraline, or trazodone may be more appropriate choices.
- A risk of excess mortality has been consistently observed in elderly patients with dementia treated with antipsychotics. The mechanism of mortality may be CV in nature (e.g. arrhythmia susceptibility from QT prolongation, increased risk of VTE). Conventional antipsychotics (e.g. haloperidol) are likely to carry a greater risk of mortality than second-generation antipsychotics (e.g. quetiapine, risperidone).
- For persistent aggression in patients with moderate to severe Alzheimer's dementia, risperidone may be used for short-term treatment only (maximum of 6 weeks) under specialist advice. The risks associated with CVA (e.g. diabetes, hypertension, smoking) should be assessed before commencing treatment with risperidone.
- Avoid the combination of risperidone and furosemide. Treatment with this combination is associated with higher mortality than with either drug alone.

- Avoid in acute porphyria.
- Use with caution in patients with:
  - CV disease (risk of postural hypotension)
  - concurrent prescription of CYP2D6 inhibitors (or known CYP2D6 poor metabolizer status) (see ➔ *Drug interactions*, p. 604)
  - dementia with Lewy bodies (increased risk of NMS)
  - diabetes (risk of hyperglycaemia in the elderly; significant weight gain reported)
  - elderly (see ➔ *Dose adjustments*, p. 605)
  - epilepsy (seizure threshold may be lowered, although the risk is relatively small)
  - hepatic/renal impairment (see ➔ *Dose adjustments*, p. 605)
  - Parkinson's disease (risperidone may interfere with treatment)
  - phenylketonuria—risperidone orodispersible tablets may contain aspartame, a source of phenylalanine.
- Concurrent use of adrenaline and antipsychotics may cause dose-dependent severe hypotension and tachycardia (the α-adrenergic antagonist effects of antipsychotics can result in decreased peripheral resistance, and adrenaline may have significant β_2-adrenergic-mediated vasodilatory effects).
- Postural hypotension may occur, especially during initiation.
- Although risperidone carries a *conditional* risk of QT prolongation/TdP,[4] the SmPC recommends caution in patients with:
  - bradycardia
  - concurrent use of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 604)
  - electrolyte disturbances, e.g. hypokalaemia, hypomagnesaemia (correct before commencing treatment)
  - known CV disease or family history of QT interval prolongation.
- Risperidone has been associated with the development of akathisia, which is most likely to occur within the first few weeks of treatment. Review continued treatment, as increasing the dose may be detrimental.
- If a patient develops signs and symptoms indicative of NMS, such as altered mental status, autonomic instability (e.g. cardiac dysrhythmia, diaphoresis), hyperpyrexia, and muscle rigidity, or presents with unexplained high fever without additional clinical manifestations of NMS, risperidone must be discontinued.
- Avoid sudden withdrawal of treatment, as this may lead to recurrence of symptoms or, rarely, acute withdrawal symptoms such as nausea, vomiting, and sweating.
- Risperidone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: extrapyramidal symptoms (dose-dependent); headache; insomnia; sedation; somnolence.
- *Common*: abdominal discomfort; abdominal pain; agitation; akathisia; anxiety; appetite changes (increase or decrease); arthralgia; blurred

vision; conjunctivitis; constipation; depression; diarrhoea; dizziness; dry mouth; dyskinesia; dyspnoea; dystonia; epistaxis; fall; hypertension; hyperprolactinaemia; influenza; oedema; nausea/vomiting; pneumonia; rash; sleep disorder; tachycardia; tremor; toothache; urinary incontinence; urinary tract infection; weight increase.

- *Uncommon*: anaemia; arrhythmias; confusion; dry eyes; dysphagia; faecal incontinence; flushing; hyperglycaemia; hypotension; hypersensitivity; joint stiffness/swelling; neutropenia; nightmares; photophobia; raised liver enzymes; reduced libido; syncope; tardive dyskinesia; tinnitus; vertigo.
- *Rare*: anaphylaxis; agranulocytosis; bowel obstruction; glaucoma; hyperinsulinaemia; hypoglycaemia; hypothermia; jaundice; NMS; pancreatitis; priapism; PE; rhabdomyolysis; SIADH; sinus arrhythmia; sleep apnoea syndrome; venous thrombosis.
- *Very rare*: angioedema; diabetic ketoacidosis; ileus.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Risperidone is metabolized mainly by CYP2D6; a minor pathway involves CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Carbamazepine* significantly reduces the plasma concentrations of both risperidone and the active metabolite (CYP3A4 induction). The dose of risperidone may need to be titrated accordingly when carbamazepine is added or discontinued.

Pharmacodynamic

- Risperidone can cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *ciprofloxacin*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Antidiabetics*—impaired glycaemic control (risk of hyperglycaemia).
- *Anti-epileptics*—may need to be increased to take account of the lowered seizure threshold.
- *Antihypertensives*—significant hypotension can develop.
- *CNS depressants*—additive sedative effect.
- *Levodopa and dopamine agonists*—effect antagonized by risperidone.
- *Levomepromazine*—increased risk of extrapyramidal symptoms.
- *Metoclopramide*—increased risk of extrapyramidal symptoms.

Unknown

- *Furosemide*—increased risk of death in elderly patients with dementia.

Dose

Psychosis

- Initial dose 1mg PO BD, increasing on the second day to 2mg PO BD. Some patients may benefit from a slower dose increase (see *Dose adjustments*, p. 605). Dose can be increased further to a usual maximum of 3mg PO BD. Higher doses are possible but should be used under expert supervision.

+Delirium

- Initial dose 500 micrograms PO BD, increased as necessary by 500 micrograms PO daily to a usual maximum of 1mg PO BD. Unusual to require higher doses.

+Refractory nausea and vomiting

- Initial dose 500 micrograms PO ON. Usual maximum dose of 1mg PO ON.

+Major depression

- Initial dose 1mg PO ON, increased to 1mg PO BD or 2mg PO ON, if necessary, after 1–2 weeks. To be used in conjunction with standard antidepressant monotherapy.

Dose adjustments

Elderly

- For psychosis and delirium, an initial dose of 500 micrograms PO BD is suggested. Increase by 500 micrograms PO OD to BD to a maximum dose of 2mg PO BD.
- For major depression, or refractory nausea and vomiting, an initial dose of 250micrograms to 500 micrograms PO ON is suggested. No more than 1mg PO ON should be necessary.

Hepatic/renal impairment

- The manufacturer advises caution in this group of patients since data are lacking. For all indications, starting and consecutive dosing should be halved, and dose titration should be slower for patients with hepatic or renal impairment.

Additional information

- Weight gain generally occurs during the first 6–12 months of treatment.
- The liquid may be mixed with water, black coffee, or orange juice prior to administration. Orodispersible tablets will begin disintegrating within seconds after placing on the tongue.
- If necessary, risperidone tablets can be crushed and dispersed in water immediately prior to use. The resulting suspension will easily pass through a nasogastric tube.
- Risk of extrapyramidal effects with risperidone is lower than with haloperidol.
- Risperidone may be a useful antiemetic for refractory nausea and vomiting (D_2 and H_1 antagonist).

Pharmacology

Risperidone is a benzisoxazole antipsychotic which acts as a 5-HT_{2A}, 5-HT_7, and D_2 receptor antagonist. The serotonin antagonism is believed to improve negative symptoms of psychoses and reduce the incidence of extrapyramidal adverse effects. Risperidone is also an antagonist at numerous receptors, including 5-HT_{2C}, α_1, α_2, and H_1 receptors, but it has no activity at muscarinic receptors. It is rapidly and well absorbed orally and extensively metabolized by CYP2D6 to the active metabolite 9-hydroxyrisperidone (paliperidone). A minor metabolic pathway involves CYP3A4, but significant induction can reduce the effectiveness of risperidone (see *Drug interactions*, p. 604). Since risperidone metabolism involves CYP2D6, the effect of drug inhibition and polymorphism must be considered if unexpected results are observed.

References

1. Caraceni A, Simonetti F. Palliating delirium in patients with cancer. *Lancet Oncol*. 2009;**10**(2):164–72.
2. Okamoto Y, Tsuneto S, Matsuda Y, *et al*. A retrospective chart review of the antiemetic effectiveness of risperidone in refractory opioid-induced nausea and vomiting in advanced cancer patients. *J Pain Symptom Manage*. 2007;**34**(2):217–22.
3. Owenby RK, Brown LT, Brown JN. Use of risperidone as augmentation treatment for major depressive disorder. *Ann Pharmacother*. 2011;**45**(1):95–100.
4. Lambiase PD, de Bono JP, Schilling RJ, *et al*. British Heart Rhythm Society clinical practice guidelines on the management of patients developing QT prolongation on antipsychotic medication. *Arrhythm Electrophysiol Rev*. 2019;**8**(3):161–5.

Rivaroxaban

Xarelto® (POM)

Tablet: 2.5mg (*light yellow*—56); 10mg (*light red*—10, 30, 100); 15mg (*red*—14, 28, 42, 100); 20mg (*brown-red*—7, 28, 100).

Indications

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, or transient ischaemic attack.
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

Contraindications and cautions

- Rivaroxaban is contraindicated for use in the following circumstances:
  - active, clinically significant bleeding
  - concomitant treatment with any other anticoagulants, except under specific circumstances or switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter
  - hepatic disease associated with coagulopathy and clinically relevant bleeding risk
  - risk of major bleed (e.g. GI ulceration—current or recent; presence of malignant neoplasms at high risk of bleeding).
- For instructions on management of bleeding—see the current edition of the *BNF*.
- The concomitant use of rivaroxaban with combined CYP3A4/P-gp inhibitors (e.g. *ketoconazole*, *posaconazole*) is not recommended due to an increased bleeding risk.
- The concomitant use of rivaroxaban with CYP3A4 inducers (e.g. *rifampicin*) is not recommended due to reduced effect. If administration cannot be avoided, the patient must be monitored for signs of thrombosis.
- Use with caution in:
  - bronchiectasis
  - combination with CYP3A4 inhibitors (see ➔ *Drug interactions*, p. 608)
  - prosthetic heart valves (efficacy not established).
- Serious skin reactions have been reported during post-marketing surveillance (see ➔ *Adverse effects*). The greatest risk of these reactions appears to be within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash.
- Refer to the SmPC for details about managing rivaroxaban prior to a procedure.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; anaemia; constipation; diarrhoea; dizziness; dyspepsia; ecchymosis; epistaxis; eye haemorrhage; GI tract haemorrhage; gingival bleeding; haemoptysis; haematoma; headache;

hypotension; increase in transaminases; nausea; peripheral oedema; post-procedural haemorrhage; pruritus; renal impairment; vomiting; urogenital tract haemorrhage; wound secretion.
- *Uncommon*: allergic dermatitis; angioedema; cerebral and intracranial haemorrhage; dry mouth; haemarthrosis; hepatic impairment; malaise; syncope; tachycardia; thrombocytopenia; thrombocytosis; urticaria.
- *Rare*: cholestasis; hepatitis; increased lactate dehydrogenase; increased lipase; increased amylase; jaundice; localized oedema; muscle haemorrhage; vascular pseudoaneurysm.
- *Very rare*: anaphylaxis; DRESS; Stevens–Johnson syndrome/toxic epidermal necrolysis.
- *Unknown*: compartment syndrome secondary to bleeding; renal failure/acute renal failure secondary to bleeding sufficient to cause hypoperfusion.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Rivaroxaban is a substrate of CYP3A4 and CYP2J2. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *CYP3A4/P-gp inhibitors (strong)*—concomitant treatment is not recommended by the manufacturer.
- *CYP3A4 inhibitors*—interaction becomes clinically significant in the presence of renal impairment (refer to the SmPC).
- The effect of *grapefruit juice* is unknown.

Pharmacodynamic
- The following drugs increase the risk of bleeding:
  - *aspirin*
  - *clopidogrel*
  - *corticosteroids*
  - *NSAIDs*
  - *SSRIs*.

Dose

Consider checking LFTs prior to initiating rivaroxaban.

Prevention of stroke and systemic embolism
- 20mg PO OD.

Treatment of DVT and PE, and prevention of recurrent DVT and PE
- Initial treatment of acute DVT or PE is 15mg PO BD for 3 weeks, followed by 20mg PO OD.

  - Treatment duration of at least 3 months should be considered if DVT or PE is provoked by major transient risk factors (i.e. recent major surgery or trauma).
  - Longer treatment duration should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.
- Extended prevention of recurrent DVT and PE (following completion of at least 6 months' therapy) with 10mg PO OD (for high-risk patients or recurrence while on 10mg PO OD, increase to 20mg PO OD).

Dose adjustments

Elderly

- No dose reductions necessary.

Hepatic/renal impairment

- Contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child–Pugh classes B and C.
- In patients with moderate (CrCl 30–49mL/min) or severe (CrCl 15–29mL/min) renal impairment, the following dose recommendations apply:
  - for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15mg OD
  - for treatment of DVT and PE and prevention of recurrent DVT and PE: patients should be treated with 15mg BD for the first 3 weeks. Thereafter, when the recommended dose is 20mg OD, a reduction of the dose from 20mg OD to 15mg OD should be considered if the patient's assessed risk of bleeding outweighs the risk of recurrent DVT and PE.
- Use is not recommended in patients with CrCl <15mL/min.

Additional information

- Tablets may be crushed and mixed with water or apple puree immediately prior to use and administered PO. The crushed tablet can also be given in a small amount of water via a gastric tube, which should be flushed after administration.
- Refer to the SmPC for information about changing from, or to, other anticoagulants.

Pharmacology

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated. Absorption of rivaroxaban is high, with an oral bioavailability of between 80% and 100%. It is a substrate of P-gp. Approximately two-thirds of a dose is metabolized, with elimination occurring equally via renal and faecal routes. The remaining one-third of the dose is renally excreted unchanged.

Rivastigmine

Exelon® (POM)

Transdermal patch: 4.6mg/24 hours (30); 9.5mg/24 hours (30); 13.3mg/24 hours (30).

Generic (POM)

Capsule: 1.5mg (28; 56); 3mg (28; 56); 4.5mg (28; 56); 6mg (28; 56).
Oral solution: 2mg/mL (120mL).
Transdermal patch: 4.6mg/24 hours (30); 9.5mg/24 hours (30); 13.3mg/24 hours (30).

Indications

- Mild to moderate dementia in Alzheimer's disease.
- Mild to moderate Parkinson's disease dementia (PO route only).
- *NB—although licensed for Parkinson's disease dementia, rivastigmine may exacerbate or induce extrapyramidal symptoms, although transdermal products are less likely to cause adverse effects.*

Contraindications and cautions

- Use with caution in patients with:
  - asthma
  - COPD
  - hepatic impairment (see ➔ *Dose adjustments*, p. 611)
  - Parkinson's disease
  - renal impairment (see ➔ *Dose adjustments*, p. 611)
  - supraventricular conduction abnormalities (may cause bradycardia)
  - susceptibility to peptic ulcers (increase in gastric acid secretion).
- Adverse effects (see ➔ *Adverse effects*) are dose-related. If treatment is interrupted for several days (e.g. due to vomiting), the dose must be retitrated to avoid the development of adverse effects.
- During therapy, the patient's weight should be monitored (rivastigmine is associated with weight loss).
- All patients receiving rivastigmine should have their ability to continue driving or operating complex machines evaluated. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- Adverse effects below have been accumulated in patients with Alzheimer's dementia or Parkinson's disease receiving *oral rivastigmine*.
- Key: a = *Alzheimer's disease*; b = *Parkinson's disease*.
  - *Very common*: anorexia[a]; diarrhoea[a]; dizziness[a]; fall[b]; nausea[a,b]; tremor[b]; vomiting[a,b].
  - *Common*: abdominal pain[a,b]; agitation[a]; anorexia[b]; anxiety[a,b]; application site reactions[b]; asthenia[a,b]; bradycardia[b]; bradykinesia[b]; confusion[a]; dehydration[b]; delirium[b]; depression[a,b]; diarrhoea[a,b]; dizziness[b]; drowsiness[a,b]; dyskinesia[b]; dyspepsia[a,b]; exacerbation of Parkinson's disease[b]; fatigue[a,b]; hallucinations[b]; headache[a,b]; hypertension[b]; insomnia[b]; nausea[b]; nightmares[a]; pyrexia[b]; rash[b];

restlessness[b]; salivary hypersecretion[b]; sweats[a,b]; tremor[a]; urinary tract infection[b]; weight decrease[a].
  - *Uncommon*: atrial fibrillation[b]; depression[a]; dystonia[b]; fall[a]; hypotension[b]; insomnia[a]; elevated LFTs[a]; syncope[a].
- Adverse effects below have been accumulated in patients with Alzheimer's dementia receiving *transdermal rivastigmine*.
  - *Common*: abdominal pain; agitation; anorexia; anxiety; application site reactions; asthenia; delirium; depression; diarrhoea; dizziness; dyspepsia; fatigue; headache; nausea; pyrexia; rash; syncope; urinary incontinence; urinary tract infection; vomiting; weight decrease.
  - *Uncommon*: aggression; bradycardia; dehydration; gastric ulcer; psychomotor hyperactivity.

Drug interactions

Pharmacokinetic

- None known. Rivastigmine does not undergo hepatic metabolism via the CYP450 system.

Pharmacodynamic

- *Anticholinergics*—may antagonize the effects.

Dose

Oral

- Initial dose 1.5mg PO BD. The dose can be increased by 1.5mg PO BD every 2 weeks according to response. The maximum dose is 6mg PO BD.
- *NB—if treatment is interrupted for more than several days, rivastigmine should be recommenced at 1.5mg PO BD and retitrated.*

Transdermal

(NB—licensed for use in mild to moderate dementia in Alzheimer's disease only)

- Initial dose 4.6mg/24-hour patch. Remove the patch after 24 hours and site the replacement on a different area of skin.
- The dose can be increased to 9.5mg/24 hours after at least 4 weeks. Further titration to 13.3mg/24 hours can be done after 6 months if clinically indicated.
- *NB—if treatment is interrupted for >3 days, rivastigmine should be recommenced at 4.6mg/24 hours and retitrated.*

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- Although plasma concentrations have been shown to increase, no dose adjustments are necessary in patients with renal or mild to moderate hepatic impairment; the dose, however, must be carefully titrated to effect. Rivastigmine can be used in patients with severe hepatic impairment, but close monitoring of treatment is required.
- The manufacturer states that there is no increased exposure to rivastigmine in patients with severe renal impairment.

Additional information

- Transdermal administration of rivastigmine is less likely to cause GI disturbances.
- If changing from oral to transdermal therapy:
  - 3mg to 6mg PO daily, initial transdermal dose is 4.6mg/24 hours (then titrate as above)
  - 9mg to 12mg PO daily, initial transdermal dose is 9.5mg/24hours.
- The first patch should be applied on the day following the last oral dose.
- Patches should be applied to clean, dry, non-hairy, non-irritated skin on the back, upper arm, or chest. The same area should be avoided for at least 14 days.

Pharmacology

Rivastigmine is an anticholinesterase inhibitor. It is rapidly and extensively metabolized primarily via cholinesterase-mediated hydrolysis.

Ropinirole

Standard-release

Adartrel® (POM)

Tablet: 250 micrograms (12); 500 micrograms (28); 2mg (28).

Requip® (POM)

Tablet: 1mg (84); 2mg (84); 5mg (84).

Generic (POM)

Tablet: 250 micrograms (12); 500 micrograms (28); 1mg (84); 2mg (28; 84); 5mg (84).

Modified-release

Requip® XL (POM)

Tablet: 2mg (28); 4mg (28); 8mg (28).

Generic (POM)

Tablet: 2mg (28); 4mg (28); 6mg (28); 8mg (28).

Indications

- Restless legs syndrome (*standard-release—see SmPC*).
- Parkinson's disease (*standard-release and modified-release—see SmPC*)

Contraindications and cautions

- The manufacturer states that ropinirole should not be used in patients with hepatic impairment or severe renal impairment (CrCl <30mL/min).
- Ropinirole should be used with caution in patients with:
  - CV disease (risk of arrhythmias and hypotension—monitor BP during initiation)
  - major psychotic disorders (antagonism between drugs)
  - renal impairment.
- Paradoxical worsening of restless legs syndrome symptoms can occur; dose adjustment or discontinuation should be considered.
- Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep.
- Behavioural symptoms of impulse control disorders and compulsions, such as binge eating and compulsive shopping, can occur. Dose reduction/tapered discontinuation should be considered.
- Taper treatment on discontinuation, as symptoms suggestive of NMS have been reported with abrupt withdrawal of dopaminergic treatment.
- The modified-release formulations are designed to deliver ropinirole over a 24-hour period. Rapid GI transit, such as diarrhoea, increases the risk of incomplete absorption.
- Ropinirole may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: drowsiness; dyskinesia (occurs during initial titration); nausea; syncope.
- *Common*: abdominal pain; confusion; constipation; dizziness; dyspepsia; hallucinations; peripheral oedema; sudden onset of sleep; vomiting.
- *Uncommon*: delirium; delusion; excessive daytime somnolence; hypotension; paranoia.
- *Unknown*: binge eating; compulsive eating; compulsive spending or buying; hypersexuality; increased libido; pathological gambling.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Ropinirole is a substrate of CYP1A2; it may inhibit CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Ciprofloxacin*—increased plasma concentrations of ropinirole.
- Smoking may increase the clearance of ropinirole. If a patient starts or stops smoking, dose adjustments may be necessary.

Pharmacodynamic

- *Alcohol*—additive sedative effect.
- *CNS depressants*—additive sedative effect.
- *Dopamine antagonists (e.g. antipsychotics, metoclopramide)*—may decrease the efficiency of ropinirole due to dopamine antagonism.

Dose

Parkinson's disease

Standard-release

- Initial dose 250 micrograms PO TDS. The dose can be increased by increments of 750 micrograms at weekly intervals to 1mg PO TDS. Further dose increases can be made in increments of up to 3mg per week.
- Usual dose range is 9mg to 16mg PO in three divided doses; maximum dose of 24mg PO daily.

Modified-release

- To be used in patients with stable Parkinson's disease transferring from a standard-release formulation.
- Initial dose is based on the previous total daily dose of a standard-release formulation. If patients are taking a different total daily dose of ropinirole standard-release tablets to those available as modified-release, they should be switched to the nearest available dose.

- If control of symptoms is not achieved or maintained:
  - in patients receiving <8mg PO OD, increase in steps of 2mg at intervals of at least 1 week to 8mg PO OD according to response
  - in patients receiving >8mg PO OD, increase in steps of 2mg at intervals of at least 2 weeks according to response to a maximum of 24mg PO OD.

Restless legs syndrome

- Initial dose 250 micrograms PO ON for 2 days, increased if tolerated to 500 micrograms PO ON for 5 days. The dose can be increased, if necessary, to 1mg PO ON for 7 days. Further dose increases of 500 micrograms/week over a 2-week period to a dose of 2mg PO OD can be made if needed. The maximum daily dose of 4mg is achieved by increasing the dose by 500 micrograms/week over a 2-week period to 3mg PO OD, followed by an additional 1mg PO OD thereafter.

Dose adjustments

Elderly

- No specific guidance available. The manufacturers state that dose increases should be gradual and titrated against the symptomatic response.

Hepatic/renal impairment

- The UK SmPC contraindicates the use of ropinirole in hepatic impairment. Nonetheless, the US SmPC states ropinirole has not been studied in patients with hepatic impairment. Given the hepatic metabolism, patients with impairment would be expected to have higher plasma levels than patients with normal hepatic function. Therefore, ropinirole should be titrated with caution in patients with mild to moderate hepatic impairment, but avoid in patients with severe hepatic impairment.
- Dose adjustment is unnecessary in patients with mild to moderate renal impairment (CrCl 30 to 50mL/min). Ropinirole is contraindicated for use in patients with severe renal impairment (CrCl <30mL/min) not receiving haemodialysis. For patients with end-stage renal disease receiving haemodialysis, recommended doses are as follows:
  - initial dose of *standard-release* ropinirole is 250 micrograms PO TDS
  - initial dose of *modified-release* ropinirole is 2mg PO OD.
- Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose is 18mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required.

Additional information

- In the management of restless legs syndrome, should treatment be interrupted for more than a few days, ropinirole should be reinitiated by dose titration, as described above (see ➔ *Dose*, p. 614).
- For patients experiencing intolerable adverse effects, downtitration followed by more gradual uptitration has been shown to be beneficial.
- Standard-release tablets can be dispersed in water immediately prior to administration if necessary.

Pharmacology

Ropinirole is a dopamine D_2 and D_3 receptor agonist. The mechanism of action of ropinirole as treatment for Parkinson's disease or restless legs syndrome is unknown, although in the former case, it is believed to be related to its ability to stimulate dopamine receptors in the striatum. Ropinirole is completely absorbed after oral administration. It is extensively metabolized by CYP1A2 to inactive metabolites that are mainly excreted in the urine.

Rotigotine ⚠

Neupro® (POM)
Transdermal patch: 1mg/24 hours (28); 2mg/24 hours (28); 3mg/24 hours (28); 4mg/24 hours (28); 6mg/24 hours (28); 8mg/24 hours (28).

Indications

- Parkinson's disease (as either monotherapy or adjunctive therapy).
- Moderate to severe restless legs syndrome.

Contraindications and cautions

- The transdermal formulation contains aluminium. To avoid skin burns, the patch must be removed if the patient is to undergo MRI or cardioversion.
- There is a presumed risk of postural hypotension—it is recommended that BP is monitored at the beginning of therapy.
- Rotigotine has been associated with somnolence and episodes of sudden sleep onset. Patients should be continually reassessed for drowsiness or sleepiness, and a dose reduction or treatment cessation considered if this is observed.
- Rotigotine may have a major influence on the ability to drive and use machines. Patients affected by somnolence and/or sudden sleep episodes must not drive or operate machines until such episodes and somnolence have resolved. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Patients should be monitored for the development of impulse control disorders. Dose reduction/tapered discontinuation should be considered if such symptoms develop.
- Symptoms suggestive of NMS have been reported with abrupt withdrawal of dopaminergic therapy. Therefore, it is recommended to taper treatment.
- External heat (excessive sunlight, heating pads, and other sources of heat such as sauna and hot bath) should not be applied to the area of the patch.
- Treatment must be discontinued gradually. To prevent withdrawal symptoms, the SmPC suggests reducing the daily dose in steps of 1mg/24 hours, with a dose reduction preferably every other day, until complete withdrawal.
- May be used in the end-of-life management of Parkinson's disease. Guidance from a specialist is strongly recommended before initiating in these circumstances.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: application and instillation site reactions (e.g. dermatitis, erythema, inflammation, pruritus, rash, vesicles); asthenia; fatigue; headache; malaise; nausea.
- *Common*: abnormal dreams; dyspepsia; hypersensitivity (including angioedema, tongue oedema, and lip oedema); hypertension; impulse control disorders (including binge eating and pathological gambling);

insomnia; irritability; peripheral oedema; pruritus; sexual desire disorders (including hypersexuality and increased libido); sleep attacks; somnolence; vomiting.
- *Uncommon*: agitation; obsessive–compulsive disorder; postural hypotension.
- *Rare*: aggressive behaviour; disorientation.
- *Unknown*: abdominal pain; arrhythmias; confusional state; constipation; delirium; delusion; deranged LFTs (i.e. increased); diarrhoea; dizziness; dopamine dysregulation syndrome; dry mouth; dyskinesia; erectile dysfunction; erythema; hiccups; hyperhidrosis; hypotension; loss of consciousness; nightmares; palpitations; paranoia; perception disturbances (including auditory and visual hallucinations); photopsia; psychotic disorder; raised liver enzymes; syncope; vertigo; visual impairment (e.g. blurred vision, photopsia); weight changes (decrease or increase).

Drug interactions

Pharmacokinetic
- There are no recognized clinically significant pharmacokinetic interactions.

Pharmacodynamic
- *Dopamine antagonists*—antagonize the effect of rotigotine; avoid concurrent use.
- *CNS depressants*—risk of additive effects.

Dose

Contact a Parkinson's disease specialist before commencing.

When converting an established Parkinson's disease patient to rotigotine patches (i.e. when approaching the end of life), consider using the OPTIMAL guideline to guide treatment (http://www.parkinsoncalculator.com/index.html).

If the patient has delirium or dementia, a lower starting dose is recommended.

Similarly, should the patient develop symptoms of delirium or exacerbations of dementia during treatment with rotigotine, consider reducing the dose in 2mg/24-hour increments.

Monotherapy in Parkinson's disease
- Initially 2mg/24 hours, then increased in steps of 2mg/24 hours, if required, up to a maximum of 8mg/24 hours.

Adjunctive therapy with co-beneldopa or co-careldopa in Parkinson's disease
- Initially 4mg/24 hours, then increased in steps of 2mg/24 hours, if required, up to a maximum of 16mg/24 hours .

Moderate to severe restless legs syndrome
- Initially 1mg/24 hours, then increased in steps of 1mg/24 hours, if required, up to a maximum of 3mg/24 hours.

Dose adjustments

Elderly

- Usual adult doses can be used. Note, however, that the elderly are more susceptible to adverse effects.

Hepatic/renal impairment

- The SmPC states that no relevant increases of rotigotine plasma levels were observed in patients with moderate hepatic impairment or mild to severe renal impairment.
- Dose adjustments are unnecessary in patients with mild to moderate hepatic impairment. The SmPC advises that rotigotine should be used with caution in patients with severe hepatic impairment and a dose reduction may be necessary.
- Dose adjustments are unnecessary in patients with mild to severe renal impairment or those requiring dialysis.

Additional information

- Patients and carers should be made aware that behavioural symptoms of impulse control disorders, including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating, can occur in patients treated with dopamine agonists, including rotigotine.

Pharmacology

Rotigotine is primarily a D_2 and D_3 dopamine agonist, with activity at D_1, D_4, and D_5 receptors. It is also an α_{2B} antagonist and a $5HT_{1A}$ agonist. It is believed to elicit its beneficial effect on Parkinson's disease by activation of D_3, D_2, and D_1 receptors of the caudate–putamen in the brain. In animal studies, agonistic activity at $5\text{-}HT_{1A}$ receptors has been shown to reduce extrapyramidal symptoms; antipsychotic drugs with $5\text{-}HT_{1A}$ agonist properties (e.g. clozapine, aripiprazole) have lower rates of such symptoms. The precise mechanism of action of rotigotine as treatment for restless legs syndrome is unknown, although it is likely to be via dopamine receptors.

Senna (sennosides)

Senokot® (P)

Tablet: 7.5mg (60).
Syrup (sugar-free): 7.5mg/5mL (150mL; 500mL).

Generic (P)

Tablet: 7.5mg (24; 60; 100; 500).
NB—senna is available as a GSL medicine, provided the maximum dose does not exceed 15mg.

Indications

- Management of constipation.

Contraindications and cautions

- Contraindicated in intestinal obstruction.
- Avoid in patients with abdominal pain of unknown origin.

Adverse effects

- May cause abdominal cramps.
- Yellow or red-brown (pH-dependent) discoloration of urine by metabolites may occur.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- No known pharmacokinetic interactions.

Pharmacodynamic

- *Anticholinergics*—antagonize the laxative effect.
- *Cyclizine*—antagonizes the laxative effect.
- *Opioids*—antagonize the laxative effect.
- *5-HT$_3$ antagonists*—antagonize the laxative effect.
- *TCAs*—antagonize the laxative effect.

Dose

- Initial dose 7.5mg to 15mg PO ON, usually in combination with a stool softener.
- Higher doses may well be necessary for patients receiving opioids, although treatment with a PAMORA may be preferable (see Chapter 2, *Management of constipation in advanced cancer*, p. 64).

Dose adjustments

Elderly

- No specific dose adjustments recommended by the manufacturer.

Hepatic/renal impairment

- No specific dose adjustments recommended by the manufacturer.

Additional information

- Laxative effect usually evident within 8–12 hours.

Pharmacology

Sennosides are inactive glycosides that pass through the large intestine where they are hydrolysed by bacteria to the active anthraquinone fraction. This stimulates peristalsis via the submucosal and myenteric nerve plexuses. Stimulant laxatives also reduce colonic water absorption. Very little reaches the systemic circulation.

Sertraline ♡

Lustral® (POM)

Tablet (scored): 50mg (28); 100mg (28).

Generic (POM)

Tablet: 50mg (28); 100mg (28).

Indications

- Depression (including anxiety).
- Obsessive–compulsive disorder.
- †Cholestatic pruritus.[1,2]
- †Delirium/agitation (including that associated with dementia).[3]

Contraindications and cautions

- Do not use with an irreversible MAOI, or within 14 days of stopping one, or at least 24 hours after discontinuation of a reversible MAOI (e.g. *moclobemide*, *linezolid*). At least 7 days should elapse after discontinuing sertraline before starting a MAOI or a reversible MAOI. The SmPC for *selegiline* states a period of *14 days* should elapse after discontinuing sertraline before starting *selegiline*.
- Note that the SmPC specifically states that *linezolid* (a weak reversible and non-selective MAOI) should not be given to patients treated with sertraline.
- Although the combination of selective MAO-B inhibitors *rasagiline* and *selegiline* with SSRIs is well tolerated, there have been case reports of serotonin syndrome. If such a combination is necessary, under the guidance of a specialist, the recommendation is to use citalopram or sertraline without exceeding recommended doses.[4]
- The SmPC warns against concomitant administration of potent CYP3A4 inhibitors (including grapefruit juice—see ➔ *Drug interactions*, p. 624).
- Serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) has been reported in patients using SSRIs. Sertraline should be discontinued immediately if this is suspected, and supportive symptomatic treatment should be initiated. Sertraline should not be used concomitantly with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 624).
- Use with caution in epilepsy. SSRIs are, however, considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy. Sertraline may affect phenytoin levels (see ➔ *Drug interactions*, p. 624).
- In addition, use with caution in:
  - diabetes (SSRIs can alter glycaemic control and may cause impaired awareness of hypoglycaemia)
  - elderly (greater risk of hyponatraemia)
  - hepatic/renal impairment (see ➔ *Dose adjustments*, p. 625)
  - glaucoma (may cause mydriasis).
- There is a *conditional* risk of QT prolongation/TdP (most reports are associated with other risk factors) with sertraline. The SmPC recommends caution in the following situations:

  - in combination with other drugs that prolong the QT interval (see → *Drug interactions*, p. 624)
  - in patients with known CV disease or a family history of QT interval prolongation.
- Patients known to be CYP2C19 poor metabolizers should be treated with caution because plasma levels of sertraline are enhanced by about 50%; similarly, drugs that inhibit CYP2C19 should be used with caution (see → *Drug interactions*, p. 624).
- Akathisia/psychomotor restlessness may occur within the first few weeks of treatment (consider discontinuing).
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Sertraline may increase the risk of haemorrhage. Use with caution in patients with bleeding disorders or with concurrent use of other drugs carrying a similar risk (see → *Drug interactions*, p. 624).
- Some patients may experience increased anxiety symptoms at the beginning of treatment. This paradoxical reaction usually subsides within 2 weeks during continued treatment. A low starting dose is advised to reduce the likelihood of this effect.
- There is an increased risk of bone fractures in patients over 50 years of age receiving SSRIs and TCAs. The mechanism is unknown.
- Avoid abrupt withdrawal, as symptoms such as anxiety, dizziness, headache, nausea, and paraesthesia can occur. Although generally mild, they can be severe in some patients. Withdrawal symptoms usually occur within the first few days of discontinuing treatment, and they usually resolve within 2 weeks, though they can persist in some patients for up to 3 months or longer. See → Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to → Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: diarrhoea; dizziness; drowsiness; dry mouth; fatigue; headache; insomnia; nausea; sexual dysfunction (male).
- *Common*: abdominal pain; agitation; anxiety; appetite changes (increase and decrease); attention disorder; chest pain; dysgeusia; dyspepsia; flatulence; hot flushes; hyperhidrosis; decreased libido; myalgia; nightmares; palpitations; paraesthesia; pharyngitis; rash; tinnitus; tremor; visual disturbances; yawning.
- *Uncommon*: alopecia; amnesia; apathy; bronchospasm; convulsion; dry skin; dysphagia; dyspnoea; epistaxis; euphoria; hallucination; hypersalivation; hypertension; malaise; migraine; mydriasis; nocturia;

oesophagitis; osteoarthritis; rhinitis; sexual dysfunction (female); speech disorder; thirst; upper respiratory tract infection; urinary retention; urticaria; weakness.
- *Rare*: abnormal liver function; diplopia; gastroenteritis; glaucoma; hiccups; hypoglycaemia; lymphadenopathy; melaena; mouth ulceration; myocardial infarction; paranoia; peripheral ischaemia; psychotic disorder; sleep walking; suicidal ideation; urinary incontinence.
- *Unknown*: abnormal bleeding; arthralgia; gynaecomastia; hepatitis; movement disorders; pancreatitis; psychomotor restlessness; serotonin syndrome (see ➔ *Drug interactions*); SIADH; Stevens–Johnson syndrome.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic
- Is a mild to moderate inhibitor of CYP2D6. Sertraline is a substrate of multiple cytochromes: CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- The SmPC advises against concomitant use of potent CYP3A4 inhibitors (e.g. clarithromycin, itraconazole).
- *Codeine*—possible reduced analgesic benefit due to CYP2D6 inhibition.
- *Fluoxetine*—risk of increased exposure to sertraline (i.e. to consider if switching to sertraline).
- *Grapefruit juice*—may considerably increase exposure to sertraline (CYP3A4 inhibition); avoid combination.
- *Haloperidol*—increased risk of adverse effects from both drugs due to CYP2D6 inhibition.
- *Itraconazole*—risk of increased exposure to sertraline.
- *Risperidone*—increased risk of adverse effects due to CYP2D6 inhibition by sertraline.
- *Phenytoin*—risk of phenytoin toxicity.
- *Tamoxifen*—possible reduced efficacy of tamoxifen; avoid combination.
- *Tramadol*—reduced analgesic benefit due to CYP2D6 inhibition.
- *TCAs*—metabolism may be inhibited by sertraline.

Pharmacodynamic
- Risk of serotonin syndrome (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 622)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *tapentadol*, *TCAs*, *tramadol*, *trazodone*.
- Sertraline is associated with a conditional risk of prolongation of the QT interval. There is a potential risk that co-administration with other drugs that prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*,

clarithromycin, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and precautions*, p. 622).
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.
- *Antidiabetics*—SSRIs may alter glycaemic control; risk of impaired awareness of hypoglycaemia.
- *Carbamazepine*—increased risk of hyponatraemia.
- *Cyproheptadine*—may reduce the antidepressant effects of sertraline.
- *Diuretics*—increased risk of hyponatraemia.
- *Lithium*—may enhance the effect of SSRIs.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).
- *NSAIDs*—increased risk of GI bleeding (potentially worse with aspirin and naproxen).
- *SNRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

Depression
- Initial dose 50mg PO OD, increased in steps of 50mg at intervals of at least 7 days, if necessary, to 200mg PO OD. Usual maintenance dose is 50mg PO OD.

Obsessive–compulsive disorder
- Initial dose 50mg PO OD, increased in steps of 50mg at intervals of at least 7 days, if necessary, to 200mg PO OD. Usual maintenance dose is 50mg PO OD.

Panic disorder/post-traumatic stress disorder/social anxiety disorder
- Initial dose 25mg PO OD for 7 days, then increased to 50mg PO OD, with further increases in steps of 50mg at intervals of at least 7 days if the response is partial and the drug is tolerated to 200mg PO OD.

†Cholestatic pruritus
- Sertraline is considered a fourth-line option in the management of cholestatic pruritus.
- Initial dose: 50mg PO OD, increased as necessary after 7 days to a usual maintenance of 75mg to 100mg PO OD. Note that the effect may be short-lived.

†Delirium/agitation
- Initial dose 25mg to 50mg PO OD, increased if necessary to 200mg PO OD.

Dose adjustments

Elderly
- The usual adult dose can be recommended.

Hepatic/renal impairment

- Sertraline is extensively metabolized in the liver. The SmPC states that a lower or less frequent dose of sertraline should be used in patients with hepatic impairment. Sertraline is not recommended for use in patients with *severe* hepatic impairment (due to lack of clinical data). SSRIs can increase the risk for GI bleeding from varices.
- Renal excretion of unchanged drug in the urine is a minor route of elimination. The SmPC states that dosing does not have to be adjusted based on the degree of renal impairment.

Additional information

- Tablets can be dispersed in water prior to administration if necessary. They do not disperse easily, however.
- Up to 10% of the Caucasian population are classified as CYP2D6 poor metabolizers, which may have implications for treatment.
- If withdrawal symptoms emerge during discontinuation, increase the dose to prevent symptoms and then start to withdraw more slowly.
- Symptoms of anxiety or panic may worsen on initial therapy. This can be minimized by using lower starting doses.
- The SSRIs sertraline and citalopram may be of use in the management of agitation and psychosis in patients with dementia.

Pharmacology

Sertraline is a potent and specific inhibitor of neuronal serotonin uptake but has little affinity for adrenergic, benzodiazepine, dopaminergic, GABA, histaminergic, muscarinic, or serotonergic receptors. At clinical doses, sertraline does impair reuptake of serotonin into platelets. Sertraline and its major metabolite are extensively metabolized through numerous pathways; the resultant metabolites are excreted in faeces and urine in equal amounts. Only a very small amount of unchanged sertraline is excreted in the urine.

References

1. Mayo MJ, Handem I, Saldana S, *et al*. Sertraline as a first-line treatment for cholestatic pruritus. *Hepatology*. 2007;**45**(3):666–74.
2. Tajiri K, Shimizu Y. Recent advances in the management of pruritus in chronic liver diseases. *World J Gastroenterol*. 2017;**23**(19):3418–26.
3. Seitz DP, Adunuri N, Gill SS, *et al*. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev*. 2011;**2**:CD008191.
4. Aboukarr A, Giudice M. Interaction between monoamine oxidase B inhibitors and selective serotonin reuptake inhibitors. *Can J Hosp Pharm*. 2018;**71**(3):196–207.

Sodium valproate

Different preparations may vary in bioavailability. It is recommended that patients should remain on the same product once treatment has been stabilized. Inclusion of the brand name on the prescription is suggested. NICE has advised that generic switching of valproate preparations is not normally recommended due to the clinical implications of possible variations in plasma concentrations.

Standard-release

Epilim® (POM)
Crushable tablet: 100mg (30, 100).
Tablet: 200mg (30, 100); 500mg (30, 100).
Liquid (sugar-free): 200mg/5mL (300mL).
Syrup: 200mg/5mL (300mL).
Injection (powder): 400mg vial (with 4mL of WFI for reconstitution).

Generic (POM)
Crushable tablet: 100mg (100).
Tablet: 200mg (100); 500mg (100).
Liquid (sugar-free): 200mg/5mL (300mL).
Injection (powder): 400mg vial (with 4mL of WFI for reconstitution).
Injection: 300mg/3mL (five ampoules); 400mg/4mL (five ampoules).
Includes branded generics.

Modified-release

Epilim Chrono® (POM)
Tablet: 200mg (30, 100); 300mg (30, 100); 500mg (100).

Epival CR® (POM)
Tablet: 300mg (100); 500mg (100).

Epilim Chronosphere® (POM)
Granules: 50mg (30); 100mg (30); 250mg (30); 500mg (30); 750mg (30); 1000mg (30).

Episenta® (POM)
Capsules: 150mg (100); 300mg (100).
Granules: 500mg (100); 1,000mg (100).

Indications

- All forms of epilepsy.
- †Neuropathic pain.[1,2]
- †Management of status epilepticus.[3]
- †Management of seizures by CSCI.[4]

Contraindications and cautions

- Sodium valproate is contraindicated for use in patients with:
  - acute hepatic disease
  - history or family history of liver dysfunction (especially drug-related)

  - porphyria
  - pregnancy (refer to the SmPC)
  - urea cycle disorders (risk of hyperammonaemia)
  - women with childbearing potential (refer to the SmPC).
- Discontinuation should normally be done gradually and under the supervision of a specialist.
- Use with caution in hepatic and renal impairment (see ➔ *Dose adjustments*, p. 631).
- Liver dysfunction is a rare complication of sodium valproate treatment and generally becomes apparent within the first 6 months of treatment (maximum period of risk is 2–12 weeks), often in patients receiving multiple anti-epileptic drugs. Liver function and FBC should be measured before starting sodium valproate and then periodically during the first 6 months of therapy (tests should include prothrombin time). A short-lived increase in liver enzymes is commonly seen, however, particularly during early treatment.
- An abnormally low prothrombin rate, particularly in association with other abnormalities (e.g. significant decrease in fibrinogen and coagulation factors, increased bilirubin level, and raised transaminases), requires cessation of sodium valproate therapy.
- Patients and carers should be instructed to report any non-specific symptoms shown below that may precede jaundice, as they are an indication for immediate discontinuation of treatment:
  - abdominal pain
  - asthenia
  - anorexia
  - drowsiness
  - malaise
  - oedema
  - vomiting.
- Should there be any concerns, however, the patient should be reassessed and additional LFTs (including prothrombin time) should be monitored until it returns to normal. Treatment must be discontinued if liver dysfunction is confirmed.
- Pancreatitis is a rarely reported adverse effect, but it has led to fatalities. Patients with nausea, vomiting, and/or acute abdominal pain should contact their doctor.
- Haematological disorders can occur with sodium valproate, with thrombocytopenia being stated as a frequent occurrence. FBC and INR are recommended before starting treatment and before surgery, or in case of spontaneous bruising or bleeding.
- Patients should be warned about weight gain that commonly occurs with sodium valproate.
- Reversible worsening of seizures or onset of new seizures can occur on initiation of sodium valproate.
- Sodium valproate may give false positive results in testing for ketones in the urine.
- Patients should be monitored for signs of suicidal ideation since anti-epileptic drugs have been associated with this behaviour.

- It may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: nausea; tremor.
- *Common*: aggression§; agitation§; alopecia (transient—regrowth begins within 6 months); anaemia; confusional state; convulsion*; deafness; diarrhoea; disturbance in attention§; dysmenorrhoea; extrapyramidal disorder; gastralgia; gingival disorder (mainly gingival hyperplasia); haemorrhage; hallucinations; headache; hypersensitivity; hyponatraemia; liver injury (raised liver enzymes may be transient during initial treatment); memory impairment; nystagmus; somnolence; stomatitis; stupor*; thrombocytopenia; vomiting; urinary incontinence; increased weight.
- *Uncommon*: amenorrhoea; angioedema; ataxia; coma*; encephalopathy; lethargy*; hair disorder (abnormal hair texture, hair colour changes, abnormal hair growth); hyperandrogenism (acne, alopecia—male pattern, hirsutism, virilism); hypothermia; leucopenia; osteopenia; osteoporosis (long-term therapy); pancreatitis; pancytopenia; paraesthesia; reversible parkinsonism; peripheral oedema; pleural effusion; rash; renal failure; SIADH.
- *Rare*: abnormal behaviour§; abnormal coagulation tests; bone marrow failure (agranulocytosis, macrocytic anaemia, macrocytosis, red cell aplasia); cognitive disorder; diplopia; DRESS; enuresis; erythema multiforme; hyperammonaemia; hypothyroidism; male infertility; myelodysplastic syndrome; obesity; polycystic ovaries; psychomotor hyperactivity§; reversible dementia; rhabdomyolysis; Stevens–Johnson syndrome; SLE; toxic epidermal necrolysis; vasculitis.
- *Very rare*: gynaecomastia.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Sodium valproate is metabolized by glucuronidation mainly via UGT1A6, UGT1A9, and UGT2B7, mitochondrial oxidation, and minimal input from CYP2A6, CYP2B6, and CYP2C9. Sodium valproate has been shown to inhibit UGTs.
- Drugs that affect UGTs (e.g. cannabidiol) would be expected to affect serum concentrations of sodium valproate.
- *Carbamazepine*—valproate may potentiate the toxic effects of carbamazepine; plasma concentrations may need monitoring during

§ Principally observed in the paediatric population.

* Associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anticonvulsants; they have been usually reversible on withdrawal of treatment or reduction of dosage.

early combined treatment; valproate plasma concentrations may be reduced.
- *Carbapenems*—reduction in plasma concentrations of valproate have been observed, occasionally resulting in seizures.
- *Diazepam*—risk of increased effect of diazepam due to plasma protein displacement.
- *Erythromycin*—plasma concentrations of valproate may be increased due to reduced metabolism.
- *Lamotrigine*—metabolism of lamotrigine reduced, potentially leading to toxicity.
- *Lorazepam*—a dose reduction by 50% of lorazepam is recommended (UGT2B15 inhibition).
- *Olanzapine*—plasma levels of olanzapine may be reduced.
- *Phenobarbital*—increased plasma concentrations due to inhibition of metabolism by valproate (reduced glucuronidation); valproate plasma concentrations may be reduced.
- *Phenytoin*—risk of phenytoin toxicity due to displacement from protein binding sites; valproate plasma concentrations may be reduced.
- *Rifampicin*—risk of reduction in plasma concentrations of valproate.
- *Warfarin*—risk of increased INR due to displacement from protein binding sites.

Pharmacodynamic
- *Antipsychotics*—seizure threshold lowered; valproate may potentiate effects (and increase the risk of certain adverse effects).
- *Antidepressants*—seizure threshold lowered; valproate may potentiate effects (and increase the risk of certain adverse effects).
- *CNS depressants*—risk of excessive sedation.
- *MAOIs*—valproate may potentiate the effect.
- *Tapentadol*—seizure threshold lowered.
- *Tramadol*—seizure threshold lowered.

Dose

Epilepsy
- Initial dose 600mg PO OD or 300mg PO BD. Dose can be increased by 150mg to 300mg daily at 3-day intervals as necessary, until control is achieved; maximum dose of 2500mg daily in divided doses.
- For IV use, also refer to the SmPC and see *Additional information*, p. 631.
- Initial dose 10mg/kg (usual range 400mg to 800mg) by IV injection over 3–5 minutes, followed by 10mg/kg in 2 to 4 divided doses by IV injection (over 3–5 minutes) or IVI. Increase by 150mg to 300mg at 3-day intervals until control is achieved; maximum dose of 2500mg daily in divided doses.
- When the PO route is unavailable, treatment can be continued at the same dose by slow IV injection (over 3–5 minutes) or IVI.

†*Neuropathic pain*
- Initial dose 150mg to 200mg modified-release PO ON. Dose can be increased by 150mg to 300mg modified-release daily every 3 days as

necessary, until control is achieved; maximum dose of 2500mg daily in divided doses (give as BD dose).
- A small case series reports success with CSCI administration:[2]
  - initial dose 200mg to 600mg/24 hours via CSCI
  - increase the dose up to *daily*, as necessary, by 300mg/24 hours to a maximum of 1500mg/24 hours.
- Other options remain the preferred choices for the management of neuropathic pain.

†*Status epilepticus*
- Check local policies.
- Suggested dose is 40mg/kg (maximum 3000mg) in 100mL of NaCl over 5 minutes.
- Subsequent treatment should be guided by local practice.
- For example:
  - if seizures have persisted for <30 minutes despite completion of the infusion, a second IV anticonvulsant should be considered (before anaesthesia)
  - if seizures respond to the initial infusion, a maintenance dose of 1000mg IV/PO BD is suggested
  - the first dose of maintenance treatment should be given as close as possible to 12 hours after the initial loading dose described above; a range of 10–14 hours is acceptable in order to allow regular maintenance treatment during daytime hours.

† *Administration by CSCI*
- When the PO route is unavailable, treatment can be continued at the same dose via CSCI. Doses of up to 1200mg/24 hours have been reported for this indication.[3]
- WFI or NaCl can be used as diluent.
- Sodium valproate has been initiated at doses of 600mg/24 hours via CSCI.

Dose adjustments

Elderly
- No specific guidance available. Dose should be determined by seizure control.

Hepatic/renal impairment
- Valproate is contraindicated for use in patients with acute hepatic impairment. If possible, use should be avoided in patients with hepatic impairment, due to the risk of hepatotoxicity. The SmPC states sodium valproate and salicylates should not be used concomitantly since they share the same metabolic pathway.
- Patients with renal impairment may need a dose reduction. Treatment should be adjusted according to clinical response, as plasma concentrations may be misleading (see ➔ *Additional information*).

Additional information

- To reconstitute powder for injection/infusion, use 3.8mL of the solvent provided; this will provide a concentration of 100mg/mL. (NB—if

the total volume of 4mL of solvent is used, due to displacement, the concentration of reconstituted sodium valproate will be 95mg/mL.)
- Administer the IVI over 60 minutes in at least 50mL of GLU *or* NaCl.
- Despite a tenuous relationship between plasma concentration and clinical response, there is a usually accepted therapeutic range of 40mg/L to 100mg/L (278micromol/L to 694micromol/L). There is a risk of toxicity with plasma concentrations above this level. If a satisfactory response is not obtained, plasma levels should be measured to determine whether or not they are within the therapeutic range.

⊰ Pharmacology

The exact mechanism of action of sodium valproate is presently unknown. It is believed that the action involves potentiation of the inhibitory action of GABA through mechanisms that affect the metabolism or synthesis of GABA. Sodium valproate is well absorbed from the GI tract and undergoes metabolism, mainly via glucuronidation (UGT1A6, UGT1A9, and UGT2B7) and mitochondrial β-oxidation. A minor metabolic pathway involves CYP enzymes, namely CYP2A6, CYP2B6, and CYP2C9. Less than 3% of a dose is excreted unchanged.

References

1. Finnerup NB, Attal N, Haroutounian S, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;**14**(2):162–73.
2. Davis C, Crispin H, Marshallsay C, Haig S, Pennell S, Jenks A. 104 Sodium valproate subcutaneous infusion; valuable adjunct in the management of neuropathic pain in palliative patients. *BMJ Support Palliat Care*. 2018;**8**:A48.
3. Chamberlain JM, Kapur J, Shinnar S, *et al*. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. *Lancet*. 2020;**395**(10231):1217–24.
4. O'Connor N, Hayden C, O'Leary N. Sodium valproate as a continuous subcutaneous infusion: a case series. *J Pain Symptom Manage*. 2017;**54**(2):e1–2.

Spironolactone

Aldactone® (POM)

Tablet: 25mg (100); 50mg (100); 100mg (28).

Generic (POM)

Tablet: 25mg (28); 50mg (28); 100mg (28).

Unlicensed special (POM)

Oral suspension (sugar-free): 25mg/5mL; 50mg/5mL.

See ➔ *Additional information*, p. 635 for supply issues.

Indications

- Congestive heart failure.
- Ascites associated with cirrhosis or malignancy.
- Nephrotic syndrome (*not discussed*).
- Primary aldosteronism (*not discussed*).

Contraindications and cautions

- Is contraindicated in patients with:
  - acute renal insufficiency
  - Addison's disease
  - anuria
  - hyperkalaemia or baseline serum K^+ >5mmol/L
  - severe renal impairment (i.e. SeCr >220micromol/L).
- Monitor U&Es status regularly. May cause hyperkalaemia, hyponatraemia, and reversible hyperchloraemic metabolic acidosis.
- Spironolactone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: hyperkalaemia.
- *Common*: AKI; breast pain (male); confusion; dizziness; gynaecomastia; malaise; muscle spasms; nausea; pruritus; rash.
- *Uncommon*: benign breast neoplasm (male); breast pain (female); electrolyte imbalance; abnormal liver function; menstrual disorder; urticaria.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- *Digoxin*—half-life of digoxin is increased by spironolactone (plasma concentration increased <30%).

Pharmacodynamic

- *ACE-Is*—increased risk of hyperkalaemia and additive hypotensive effect.

- *Angiotensin II antagonists*—increased risk of hyperkalaemia and additive hypotensive effect.
- *Co-trimoxazole*—increased risk of hyperkalaemia.
- *NSAIDs*—may attenuate the natriuretic efficacy of diuretics due to inhibition of intrarenal synthesis of prostaglandins.
- *Potassium-sparing diuretics*—increased risk of hyperkalaemia and additive hypotensive effect.
- *Potassium supplements*—increased risk of hyperkalaemia.
- *Trimethoprim*—increased risk of hyperkalaemia.

Dose

It is recommended that doses are taken with or after food. Renal function should be closely monitored during treatment. There is a lag of 3–5 days between initiation of spironolactone and the onset of the natriuretic effect.

Heart failure with oedema

- Spironolactone should only be used in moderate to severe heart failure on the recommendation of specialist advice. There is no evidence that spironolactone is particularly effective in mild heart failure.
- Initial dose 100mg PO daily, in single or divided doses, is recommended. However, lower initial doses may be considered, with a range of 25mg to 200mg PO daily.

Severe heart failure (NYHA classes III–IV)

- In conjunction with standard therapy, 25mg PO OD if K^+ is ≤5.0mmol/L and SeCr is ≤220micromol/L.
- Dose can be increased to 50mg PO OD as necessary.
- If 25mg PO OD is not tolerated, dose can be reduced to 25mg PO ALT DIE.
- Check U&Es 1 week after initiation or increase in dose, monthly for the first 3 months, quarterly for a year, and then 6-monthly thereafter.
- If K^+ is ≥5.0mmol/L or creatinine ≥350micromol/L, stop spironolactone immediately and seek specialist advice.

Ascites (in malignancy)

- Initial dose 100mg PO OM. Increase as necessary in 100mg increments every 3–5 days, to a maximum of 400mg PO daily (in divided doses to reduce the risk of nausea). Once controlled, maintenance treatment should be individually determined.

Ascites (cirrhosis with oedema)

- If urinary Na^+/K^+ ratio is >1.0, use 100mg PO OD.
- If urinary Na^+/K^+ ratio is <1.0, use 200mg to 400mg PO daily in divided doses.
- Once controlled, maintenance treatment should be individually determined.

Dose adjustments

Elderly

- No specific guidance available. Dose requirements should be individually titrated.

Hepatic/renal impairment

- No specific guidance available. Dose requirements should be individually titrated. Severe hepatic and renal impairment may affect metabolism and excretion.

Additional information

- Spironolactone can interfere with digoxin assays.
- Excessive liquorice intake could reduce the effectiveness of spironolactone.
- An oral suspension is available from Rosemont Pharmaceuticals Ltd as an unlicensed special (Tel: 0113 244 1999).
- Tablets may be dispersed in water immediately prior to use if necessary.
- Advise patients not to self-medicate with NSAIDs.
- As with all diuretics, if vomiting or diarrhoea develops, the patient should stop taking spironolactone and speak to a doctor.

Pharmacology

Spironolactone is a specific antagonist of aldosterone, acting primarily at aldosterone-dependent Na^+-K^+ pumps in the distal convoluted renal tubule. It causes increased Na^+ and water excretion, while preserving K^+. Spironolactone has a gradual onset of action that may take up to a week before effects are seen. Spironolactone is rapidly metabolized, possibly to at least two active metabolites, which are mainly eliminated renally, with some appearing in bile.

Sucralfate

Antepsin® (POM)

Tablet (scored): 1g (50).
Suspension: 1g/5mL (250mL).

Indications

- Treatment of duodenal and gastric ulcers.
- Chronic gastritis.
- Prophylaxis of GI haemorrhage from stress ulceration.
- [+]Surface bleeding.

Contraindications and cautions

- Use with caution in patients with renal impairment (see ➔ *Dose adjustments*, p. 637).
- Sucralfate may modify reactions and patients should be advised not to drive (or operate machinery) if affected.
- Bezoars (insoluble mass in the intestine) have been reported, especially in the seriously ill or those receiving enteral feeds.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- back pain; bezoar formation (see ➔ *Contraindications and cautions*); constipation (most common complaint); diarrhoea; dizziness; drowsiness; dry mouth; flatulence; gastric discomfort; headache; hypersensitivity; indigestion; nausea/vomiting; rash; vertigo.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Sucralfate can affect the absorption of several drugs (see below); administration should be separated by 2 hours:
  - ciprofloxacin
  - digoxin
  - furosemide
  - ketoconazole
  - levothyroxine
  - phenytoin
  - ranitidine
  - tetracycline
  - theophylline
  - warfarin.
- Other drugs may be affected; if there are unexpected outcomes, consider separating administration by 2 hours.
- Sucralfate and enteral feeds by nasogastric tube should be separated by 1 hour in order to prevent bezoar formation.

Pharmacodynamic

- No known pharmacodynamic interactions.

Dose

Treatment of duodenal and gastric ulcers and chronic gastritis

- 2g PO BD (on rising and at bedtime) or 1g PO QDS 1 hour before meals and at bedtime.
- Should be taken for 4–6 weeks or, in resistant cases, up to 12 weeks.
- Dose can be increased, if necessary, to a maximum of 8g daily.

Prophylaxis of stress ulceration

- Usual dose 1g PO six times a day; can be increased to a maximum of 8g PO daily.

+Surface bleeding

- 1g to 2g PO BD (as suspension) rinsed around the mouth for oral bleeding.
- 2g (crushed tablets) in a suitable agent (e.g. *Intrasite® gel*) for bleeding wounds (other alternatives may be preferred, e.g. adrenaline, tranexamic acid).

Dose adjustments

Elderly

- No specific adjustments are required, but the lowest effective dose should be used.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. Use the lowest effective dose.
- The manufacturer recommends sucralfate should be used with extreme caution and only for short-term treatment in patients with severe renal impairment. This is unlikely to apply to topical use (surface bleeding).

Additional information

- Tablets can be crushed and dispersed in water if necessary.

Pharmacology

Sucralfate is a complex of sucrose and aluminium sulfate. In solutions with a low pH (e.g. gastric acid), it forms a thick paste that has a strong negative charge. It then binds to exposed positively charged proteins located within or around ulcers to form a physical barrier, protecting the ulcer from further direct injury. Sucralfate is poorly absorbed from the GI tract. Any amounts that are absorbed are excreted primarily in the urine.

Further reading

Masuelli L, Tumino G, Turriziani M, Modesti A, Bei R. Topical use of sucralfate in epithelial wound healing: clinical evidences and molecular mechanisms of action. *Recent Pat Inflamm Allergy Drug Discov*. 2010;**4**(1):25–36.

Tamoxifen ♡

Generic (POM)

Tablet: 10mg (30); 20mg (30).
Oral solution: 10mg/5mL (150mL).

Indications

- Breast cancer.
- Anovulatory infertility.

Contraindications and cautions

- Tamoxifen is linked to an increased risk of endometrial changes, including hyperplasia, polyps, cancer, and uterine sarcoma. Any patient with unexpected or abnormal gynaecological symptoms, especially vaginal bleeding, should be investigated.
- There is a 2–3 times increase in the risk of VTE in patients taking tamoxifen. Long-term anticoagulant prophylaxis may be necessary for some patients who have multiple risk factors for VTE.
- Increased bone pain, tumour pain, and local disease flare are sometimes associated with a good tumour response shortly after starting tamoxifen and generally subside rapidly.
- Avoid combination with CYP2D6 inhibitors because these may interact with tamoxifen, resulting in a poorer clinical outcome (see ➔ *Drug interactions*, p. 639). Patients with a CYP2D6 poor metabolizer status may also have a poor response to treatment.
- There is a *possible* risk of QT prolongation/TdP. The SmPC advises that tamoxifen may be associated with prolongation of the QT interval when given at several times the standard dose (which may occur if given with CYP2D6 inhibitors).

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: fatigue; fluid retention; hot flushes; nausea; rash; vaginal discharge/bleeding.
- *Common*: alopecia; anaemia; constipation; diarrhoea; endometrial changes (e.g. hyperplasia, polyps); headache; hypersensitivity reactions; ischaemic cerebrovascular events; leg cramps; LFT changes; light-headedness; myalgia; pruritus vulvae; sensory disturbances (e.g. dysgeusia, paraesthesia); thromboembolic events (e.g. DVT, PE—risk increased when used in combination with cytotoxic agents); tumour pain (e.g. worsening bone metastasis pain); uterine fibroids; visual disturbances (e.g. cataracts, retinopathy—mainly in patients treated with exceptionally high doses for a long period of time); vomiting.
- *Uncommon*: cirrhosis of the liver; endometrial cancer; hypercalcaemia on initiation of treatment (in patients with bone metastases); interstitial pneumonitis; leucopenia; pancreatitis; thrombocytopenia.
- *Rare*: agranulocytosis; angioedema; bullous pemphigoid; endometriosis; erythema multiforme; hepatitis; neutropenia; optic neuritis; Stevens–Johnson syndrome; uterine sarcoma; vaginal polyps; visual disturbances

(e.g. corneal changes, optic neuropathy—mainly in patients treated with exceptionally high doses for a long period of time).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Tamoxifen is a major substrate of CYP2D6, CYP3A4, and CYP3A5. Other cytochromes such as CYP2B6, CYP2C9, and CYP2C19 are involved to a lesser extent. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Co-administration with certain CYP2D6 inhibitors (e.g. *paroxetine*) has been shown to reduce the plasma levels of the potent anti-oestrogen endoxifen. The precise clinical significance of this interaction is presently unknown, but the MHRA advises co-administration of CYP2D6 inhibitors should be avoided. Patients who are CYP2D6 poor metabolizers may have possibly poorer-than-expected outcomes with tamoxifen. Higher plasma levels are associated with prolongation of the QT interval.

Pharmacodynamic

- At usual doses, in the absence of CYP2D6 inhibitors or pharmacogenetic variations, the use of tamoxifen concurrently with other agents known to prolong the QT interval is likely to be of low risk for causing clinically significant QT prolongation, especially at a dose of 20mg PO OD.
- *Warfarin*—increased anticoagulant sensitivity. Mechanism unknown.

Dose

Breast cancer

- 20mg PO OD. No evidence exists for superiority of higher doses.

Dose adjustments

Elderly

- Usual adult doses can be used.

Hepatic/renal impairment

- No specific guidance is available for use in hepatic impairment. In view of the extensive metabolism of tamoxifen, the patient may be more susceptible to adverse effects and/or treatment failure.
- No dose adjustments are necessary for patients with renal impairment.

Pharmacology

Tamoxifen is a non-steroidal anti-oestrogen that has both oestrogen antagonist and agonist activity. It acts as an antagonist on breast tissue, and as an agonist in the endometrium, bone, and lipids. The precise mechanism

of action is unknown, but the effect of tamoxifen is mediated by its metabolites 4-hydroxytamoxifen and endoxifen. The metabolism of tamoxifen is complex, involving numerous polymorphic enzymes and transport proteins. Most of a dose of tamoxifen is primarily metabolized by CYP3A4 and CYP3A5. Subsequent metabolism by CYP2D6 is believed to be involved in the important step leading to the formation of the active metabolite endoxifen.

Tapentadol

Standard-release

Palexia® (CD2 POM)

Tablet: 50mg (28; 56); 75mg (28; 56).
Oral solution: 20mg/mL (*clear/colourless*—100mL; 200mL); pH 3.5–4.5 (discard 6 weeks after opening).

Modified-release

Palexia SR® (CD2 POM)

Tablet: 50mg (*white*—28; 56); 100mg (*pale yellow*—28; 56); 150mg (*pale pink*—56); 200mg (*pale orange*—56); 250mg (*brownish-red*—56).

Ationdo SR® (CD2 POM)

Tablet: 25mg (*brownish-orange*—56); 50mg (*white*—56); 100mg (*pale yellow*—56); 150mg (*pale pink*—56); 200mg (*pale orange*—56); 250mg (*brownish-red*—56).

Indications

- Management of severe chronic pain that can be adequately managed only with opioid analgesics (*Palexia SR®*).
- Relief of moderate to severe acute pain which can be adequately managed only with opioid analgesics (*Palexia®*).

Contraindications and cautions

- There have been sporadic reports of serotonin syndrome that have involved tapentadol. Despite having very weak serotonergic activity at clinical doses, the SmPC advises that tapentadol is contraindicated for use in:
  - acute intoxication of CNS depressants, including alcohol
  - acute or severe asthma
  - hypercapnia (e.g. patients with raised intracranial pressure)
  - paralytic ileus
  - respiratory depression.
- Do not use with a MAOI, or within 14 days of stopping one (see ➔ *Drug interactions*, p. 643).
- There have been sporadic reports of serotonin syndrome that have involved tapentadol. Despite having very weak serotonergic activity at clinical doses, the SmPC advises that tapentadol should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 643). There is a risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when tapentadol is used concomitantly with other serotonergic drugs (a small number of case reports). Treatment must be reviewed urgently if symptoms develop, tapentadol should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of tapentadol and benzodiazepines (or *zopiclone/zolpidem*) increases the risk of sedation, respiratory depression,

coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.

- Use with caution in epilepsy. There have been a small number of case reports describing seizures. Tapentadol should be used cautiously with other drugs that reduce the seizure threshold (see ➔ *Drug interactions*, p. 643).
- In addition, use with caution in:
  - brain tumour or head injury (risk of raised intracranial pressure)
  - hepatic impairment (see ➔ *Dose adjustments*, p. 644)
  - patients at risk of spasm of the sphincter of Oddi (e.g. acute pancreatitis, biliary disease, cholecystectomy)
  - renal impairment (see ➔ *Dose adjustments*, p. 644).
- Although no specific or significant issues have been identified upon abrupt withdrawal, the manufacturer recommends that the dose is gradually tapered upon discontinuation.
- Tapentadol may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Results from three randomized, placebo-controlled studies showed that the effects of tapentadol on testosterone and luteinizing hormone and/or follicle-stimulating hormone are minimal and not clinically relevant.[2]
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid. This is termed opioid-induced hyperalgesia (OIH). Pain associated with OIH tends to be more diffuse than the pre-existing pain and less defined in quality. The risk of developing OIH depends not only on the dose of opioid taken, but also on factors such as gender, age, genotype, and cause of pain, i.e. each case will be unique. Management of OIH can involve changing the opioid, a reduction in the dose (by 25–50%), and addition of non-opioid analgesics such as ketamine or pregabalin/gabapentin. OIH is not specifically mentioned in the SmPC. Given the dual actions of tapentadol, the propensity to cause this effect, compared to other opioids, is unknown (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: constipation; dizziness; drowsiness; headache; nausea.
- *Common*: anxiety; reduced appetite; asthenia; attention disturbances; diarrhoea; dyspepsia; dyspnoea; fatigue; flushing; hyperhidrosis; mucosal dryness; nervousness; oedema; restlessness; pruritus; rash; sleep disorder; tremor; vomiting; weakness.

- *Uncommon*: abnormal dreams; agitation; balance disorder; confusional state; dysarthria; euphoria; hypoaesthesia; hypotension; irritability; loss of weight; memory impairment; palpitations; paraesthesia; perception disturbances; sexual dysfunction; urticaria; visual disturbance; withdrawal syndrome (see ➔ *Additional information*, p. 644).
- *Rare*: abnormal thinking; convulsions; impaired gastric emptying; respiratory depression.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Tapentadol is primarily metabolized by UGTs (UGT1A6, UGT1A9, and UGT2B7 isoforms); minor amounts (15%) are metabolized by CYP2C9, CYP2C19, and CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Alcohol*—increased plasma levels of tapentadol reported for the US modified-release product *Nucynta® ER*. This *does not* affect the UK modified-release products *Ationdo® SR* or *Palexia® SR*.
- *Cannabidiol*—theoretical interaction as cannabidiol is a UGT2B7 inhibitor.
- *Ketoconazole*—possible risk of increased effect due to inhibition of UGT2B7.
- *Phenobarbital*—possible risk of reduced analgesia.
- *Rifampicin*—possible risk of reduced analgesia.

Pharmacodynamic

- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 641)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *SSRIs*, *TCAs*, *trazodone*.
- *Antihypertensives*—increased risk of hypotension.
- *Benzodiazepines*—see ➔ *Contraindications and cautions*, p. 641.
- *CNS depressants*—risk of excessive sedation (see ➔ *Contraindications and cautions*, p. 641).
- *Gabapentin/pregabalin*—possible opioid-sparing effect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Haloperidol*—may be an additive hypotensive effect.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of tapentadol may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).
- *SNRIs/SSRIs*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).

- *Trazodone*—increased risk of seizures (and serotonin toxicity).
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 641.

Dose

NB—the shell of the tablet may be present in faeces, which has no clinical relevance.

The initial dose of tapentadol depends upon the patient's previous opioid requirements. Refer to ➔ *Additional information*.

Standard-release

- Initial dose is 50mg PO, with an additional dose permissible after 1 hour if pain control is not achieved on the *first* day of treatment. The dose should then be titrated individually, utilizing either the 50mg or 75mg tablet every 4–6 hours until a stable dose is attained.
- A maximum dose of 700mg may be given on the *first* day. Maintenance daily doses of >600mg tapentadol have not been studied and are therefore not recommended.

Modified-release

- For opioid-naïve patients, initial dose is 50mg PO BD. The dose can then be titrated, as necessary, in increments of 50mg BD *every 3 days*. Doses >250mg PO BD are presently not recommended.

Dose adjustments

Elderly

- Dose adjustments are unnecessary based on age alone.

Hepatic/renal impairment

- Patients with mild hepatic impairment do not need any dosage adjustments. In patients with moderate hepatic impairment, an initial dose of *Palexia® SR* 50mg PO OD, or *Palexia®* 50mg PO 8-hourly, is recommended, with further dose increases as necessary. The SmPC states there is no information for patients with severe hepatic impairment and as such, use is not recommended.
- Patients with mild or moderate renal impairment do not need a dosage adjustment. The SmPC states there is no information for patients with severe renal impairment and as such, use is not recommended. Note that tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys, with only 3% of a dose excreted in the urine as unchanged active substance. The metabolites have no analgesic activity.

Additional information

- Anecdotal reports suggest addition of tapentadol to a regimen comprising a more potent opioid may produce a synergistic effect, such that lower doses of the more potent opioid could be used. Tramadol has been reported to have a similar effect.
- Tapentadol has an 18-fold lower binding affinity to the human MOR than morphine, yet the analgesic potency of tapentadol is only 2–3 times lower than that of morphine in animal models.
- Tapentadol 100mg PO is considered to produce similar analgesia to morphine 30mg to 40mg PO and oxycodone 20mg to 30mg PO.

- When converting *from* morphine or oxycodone (or other opioids) *to* tapentadol, although analgesic benefit has been demonstrated, the patient should be warned that there is a risk of an opioid withdrawal syndrome, due to the lower affinity of tapentadol for the MOR.
- Caution is advised when switching a patient *from* tapentadol *to* a conventional opioid such as morphine or oxycodone. Although an equianalgesic dose can be calculated, the prescriber must consider the fact that tapentadol has a lower affinity for the MOR; converting directly to the equianalgesic dose of the opioid may result in serious opioid-related adverse effects. Cross-titration is recommended,[3] although if this is not practical, a reduced equianalgesic dose of opioid should be prescribed (e.g. 50%), with the understanding that dose increases may be necessary.
- Refer to Chapter 2, *Equianalgesia and opioid switch*, p. 56 for further information regarding opioid dose equivalences.
- *Palexia® SR* must be swallowed whole, not divided or chewed.

Pharmacology

Tapentadol is the first of a new class of drug called MOR-NRI (MOR agonist–noradrenaline reuptake inhibitor). It is a novel analgesic that combines two mechanisms of action. Unlike tramadol, tapentadol does not require metabolic activation; there is no relevant serotonin activity at clinical doses, and it exists only as a single enantiomer. The two distinct pharmacological profiles may explain the efficacy demonstrated in nociceptive and neuropathic pains. Tapentadol is subject to extensive first-pass metabolism, such that mean oral bioavailability is only 32%. The major metabolic pathway is glucuronidation via UGTs (UGT1A6, UGT1A9, and UGT2B7 isoforms), with some minor metabolic routes involving CYP2C9, CYP2C19, and CYP2D6. The metabolites are devoid of analgesic activity. Steady-state serum concentrations are achieved within 48 hours of initiating a new dose.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
2. Pergolizzi JV Jr, Breve F, Taylor R Jr, Raffa RB, Strasburger SE, LeQuang JA. Considering tapentadol as a first-line analgesic: 14 questions. *Pain Manag*. 2017;**7**(4):331–9.
3. Webster LR, Fine PG. Overdose deaths demand a new paradigm for opioid rotation. *Pain Med*. 2012;**13**(4):571–4.

Temazepam

Generic (CD3 POM)

Tablet: 10mg (28); 20mg (28).
Oral solution: 10mg/5mL (300mL).
Sugar-free formulations are available.
NB—discard 3 months after opening.

Indications

- Short-term treatment of sleep disturbances (not exceeding 4 weeks).

Contraindications and cautions

- Temazepam is contraindicated for use in patients with the following conditions:
  - acute narrow-angle glaucoma (has mild anticholinergic activity)
  - mild anxiety states
  - myasthenia gravis
  - phobic or obsessional state
  - severe hepatic insufficiency
  - severe respiratory insufficiency
  - sleep apnoea syndrome.
- Temazepam should not be used alone in the treatment of depression or anxiety associated with depression, due to the risk of precipitation of suicide.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of diazepam and opioids increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution if there is a history of drug or alcohol abuse.
- Dose reductions may be necessary in the elderly (see ➔ *Dose adjustments*, p. 647).
- Tolerance may develop after several weeks of repeated dosing.
- Avoid abrupt withdrawal, even if short-duration treatment. The risk of dependence increases with dose and duration of treatment. Prolonged use of benzodiazepines may result in the development of dependence, with subsequent withdrawal symptoms on cessation of use, e.g. agitation, anxiety, confusion, headaches, restlessness, sleep disturbances (e.g. broken sleep with vivid dreams; may persist for several weeks after withdrawal), sweating, tremor. Gradual withdrawal is advised.
- Each 5mL of oral solution contains 400mg of ethanol.
- Temazepam may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- anterograde amnesia; ataxia; confusion; depression; dizziness; drowsiness; dry mouth; fatigue; hallucinations; headache; muscle weakness; nightmares; paradoxical events (e.g. agitation, irritability, restlessness); respiratory depression; sexual dysfunction; sleep disturbance; visual disturbances.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is mainly metabolized by glucuronidation via UGT2B7. It is also a minor substrate of CYP2C19 and CYP3A4/5. Drugs that affect the CYP450 system are unlikely to impact on the pharmacokinetics of temazepam. As such, pharmacokinetic interactions are likely to be minimal in comparison to other benzodiazepines.
- *Cannabidiol*—theoretical risk of increased temazepam effects since cannabidiol is a UGT2B7 inhibitor.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Alcohol*—may precipitate seizures.
- *Baclofen*—increased risk of sedation.
- *CNS depressants*—additive sedative effect.
- *Opioids*—see *Contraindications and cautions*, p. 646.

Dose

- 10mg to 20mg PO ON. This can be increased to 30mg to 40mg PO ON as necessary.

Dose adjustments

Elderly

- Half the usual adult dose is suggested.

Hepatic/renal impairment

- No specific guidance is available. The dose of temazepam must be carefully adjusted to individual requirements.

Additional information

- Tablets may be crushed and dispersed in water immediately prior to administration if necessary.

Pharmacology

The exact mechanism of action is unknown, but it is believed to act as a modulator of the $GABA_A$ receptor, thereby enhancing GABA-ergic transmission in the CNS. Temazepam is metabolized primarily by glucuronidation via UGT2B7 to the O-conjugate of temazepam, whereas

<5% is metabolized via CYP2C19 and CYP3A4 to oxazepam, and then its glucuronides by UGT1A9 and UGT2B15. Enterohepatic recirculation of temazepam is anticipated.

Reference

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.

Thalidomide ⚠

Thalidomide Celgene® (POM)

Capsule: 50mg (28).

Talidex® (POM)

Capsule: 25mg (30).

Indications

- Multiple myeloma.
- †Cancer cachexia.[1]
- †Paraneoplastic sweating.[2,3]
- †Management of tumour-related gastric bleeding.[4]

Contraindications and cautions

- Must not be used in the following circumstances:
  - pregnant women
  - women of childbearing potential (see the SmPC).
- The conditions relating to pregnancy prevention (see the SmPC) must be fulfilled for all male and female patients.
- For women of childbearing potential, prescriptions for thalidomide should not exceed 4 weeks. Dispensing should occur within 7 days of the date of issue. For other patients, supply should be limited to 12 weeks.
- Thromboembolism and peripheral neuropathy have been reported to occur with thalidomide. Use cautiously with drugs that may increase the risk of thromboembolism or peripheral neuropathy (see ➔ *Drug interactions*, p. 650).
- Unused capsules should be returned to a pharmacy.
- Thalidomide may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

- Patients prescribed thalidomide are at increased risk of arterial and venous thromboembolism (including cerebrovascular events, DVT, myocardial infarction, and PE). Thromboprophylaxis should be administered for at least the first 5 months of treatment, especially in patients with additional thrombotic risk factors (e.g. LMWH, warfarin). Thalidomide must be discontinued if the patient experiences a thromboembolic event. Once the patient is stabilized on appropriate anticoagulant treatment, thalidomide can be restarted. The anticoagulant must be continued throughout the course of thalidomide treatment.
- Peripheral neuropathy can present with the following symptoms:
  - abnormal coordination
  - dysaesthesia
  - paraesthesia
  - weakness.
- Patients presenting with these symptoms should be assessed according to the SmPC. Treatment may be withheld or discontinued.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: anaemia; constipation; dizziness; dysaesthesia; leucopenia; lymphopenia; neutropenia; paraesthesia; peripheral neuropathy; peripheral oedema; somnolence; thrombocytopenia; tremor.
- *Common*: asthenia; bradycardia; bronchopneumopathy; cardiac failure; confusion; convulsions; DVT; depression; dry mouth; dry skin; dyspnoea; febrile neutropenia; hearing impairment; interstitial lung disease; malaise; nausea/vomiting; pancytopenia; PE; pyrexia; rash; renal failure; toxic skin eruptions; weakness.
- *Uncommon*: atrial fibrillation; atrioventricular block; intestinal obstruction; myocardial infarction.
- *Not known*: allergic reactions* (hypersensitivity, angioedema, urticaria); GI haemorrhage and/or perforation; hepatic disorders; hypothyroidism; pancreatitis; Parkinson's syndrome deterioration; posterior reversible encephalopathy syndrome (e.g. visual disturbance, headache, seizures); pulmonary hypertension; sexual dysfunction; Stevens–Johnson syndrome; toxic epidermal necrolysis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Thalidomide does not appear to be metabolized by the liver. Clinically significant pharmacokinetic drug interactions have not been reported.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Antiarrhythmics*—increased risk of bradycardia.
- *Bisphosphonates*—increased risk of renal impairment (in treatment of multiple myeloma).
- *CNS depressants*—risk of excessive sedation.
- *Dexamethasone*—may increase the risk of toxic skin reactions, immunosuppression, and thromboembolic events.
- *Epoetins*—increased risk of thromboembolic events.
- *NSAIDs*—theoretical increased risk of thromboembolic events.

Dose

Multiple myeloma

- 200mg PO ON for 6-week cycle. Patients can receive a maximum of 12 cycles.

* A delayed hypersensitivity disorder (known as hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms—DRESS) may occur at any time during treatment with symptoms such as abnormal LFTs, arthralgia, fever, rashes, and vasculitis. If such reactions do occur, thalidomide should be withdrawn immediately and permanently.

[+]Cancer cachexia
- 50mg to 100mg PO ON. Further dose increases up to 200mg PO ON may be considered.

[+]Paraneoplastic sweating
- 50mg to 100mg PO ON. Further dose increases up to 200mg PO ON may be considered.

[+]Management of tumour-related gastric bleeding
- 100mg to 300mg PO ON.
- Used in combination with other agents such as sucralfate and PPIs.

Dose adjustments

Elderly
- No dose adjustments are necessary.

Hepatic/renal impairment
- There are no specific instructions for dose adjustment in hepatic or renal impairment. The lowest effective dose should be prescribed, and the patient should be closely monitored.

Additional information

- The capsule must not be broken/opened; it must be swallowed whole.

Pharmacology

Thalidomide is an immunomodulatory agent that also has anti-inflammatory and antiangiogenic properties. The mechanism of action of thalidomide is not completely understood, although it has been shown to inhibit the synthesis of TNF-α and modulates the effects of other cytokines. The exact metabolic pathway of thalidomide is unknown; it is believed not to involve the cytochrome P450 system but also undergoes non-enzymatic hydrolysis in plasma.

References

1. Davis M, Lasheen W, Walsh D, *et al*. A phase II dose titration study of thalidomide for cancer-associated anorexia. *J Pain Symptom Manage*. 2012;**43**(1):78–86.
2. Deaner PB. The use of thalidomide in the management of severe sweating in patients with advanced malignancy: trial report. *Palliat Med*. 2000;**14**(5):429–31.
3. Calder K, Bruera E. Thalidomide for night sweats in patients with advanced cancer. *Palliat Med*. 2000;**14**(1):77–8.
4. Lambert K, Ward J. The use of thalidomide in the management of bleeding from a gastric cancer. *Palliat Med*. 2009;**23**(5):473–5.

Theophylline

Standard-release

Unlicensed special **(P)**

Liquid: 50mg/5mL (300mL).

Modified-release

Uniphyllin® (P)

Tablet (scored): 200mg (56); 300mg (56); 400mg (56).

Indications

- Prophylaxis and treatment of reversible bronchospasm.

Contraindications and cautions

- Contraindicated for use in patients with porphyria.
- Potentially serious hypokalaemia may result from theophylline treatment, particularly if used in combination with β_2-agonists, corticosteroids, and diuretics.
- Use with caution in the following circumstances:
  - acute febrile illness
  - cardiac arrhythmias
  - chronic alcoholism
  - congestive heart failure (increased half-llife)
  - elderly (increased half-life)
  - hepatic impairment (increased half-life)
  - hyperthyroidism
  - peptic ulcer
  - severe hypertension.

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- abdominal discomfort; diarrhoea; gastric irritation; headache; hypotension; insomnia; nausea/vomiting; palpitations.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is a major substrate of CYP1A2; it is also metabolized by CYP3A4, CYP2E1, and xanthine oxidase to a lesser extent. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Theophylline may be affected by many drugs; several interactions are listed below, but refer to ➔ *Cytochrome P450 tables* on the inside back cover for a list of drugs that may potentially affect theophylline.

- *Allopurinol*—may increase the plasma concentration of theophylline.
- *Amiodarone*—may increase the plasma concentration of theophylline.
- *Carbamazepine*—reduces the plasma concentration of theophylline.
- *Ciprofloxacin*—can increase the plasma concentration of theophylline.
- *Erythromycin*—can increase the plasma concentration of theophylline.
- *Phenobarbital*—reduces the plasma concentration of theophylline.
- *Phenytoin*—reduces the plasma concentration of theophylline.
- *Rifampicin*—reduces the plasma concentration of theophylline.
- Note that smoking and chronic alcohol consumption increase the clearance of theophylline (induce CYP1A2/CYP2E1). If a patient stops smoking, ensure the dose of theophylline is closely monitored (see Box 1.11).

Pharmacodynamic

- *β_2-agonists*—increased risk of hypokalaemia.
- *Corticosteroids*—increased risk of hypokalaemia.
- *Diuretics*—increased risk of hypokalaemia.

Dose

Standard-release

- Usually initiate treatment with the modified-release formulation and use liquid for patients with difficulty swallowing. Administer TDS. When converting to liquid, monitor plasma concentrations.

Modified-release

- Initial dose 200mg PO BD. The dose is adjusted according to plasma concentrations.

Dose adjustments

Elderly

- The lowest initial doses should be prescribed, with dose adjustments occurring based on plasma concentrations.

Hepatic/renal impairment

- Theophylline is hepatically metabolized. Although no information exists, it is advisable to initiate treatment with low doses, with close monitoring of plasma concentrations.
- No dose adjustments should be necessary in renal impairment.

Additional information

- Theophylline plasma concentration for optimum response is 10mg/L to 20mg/L (55micromol/L to 110micromol/L). Samples should be taken 4–6 hours after a dose and at least 5 days after starting treatment. There is a narrow margin between therapeutic and toxic dose.
- Unlicensed liquid formulation is available from a variety of manufacturers.

Pharmacology

Theophylline is a xanthine derivative that is chemically similar to caffeine. It competitively inhibits type III and IV phosphodiesterase and also binds to the adenosine A_2B receptor, blocking adenosine-mediated bronchoconstriction. It is rapidly and completely absorbed after oral administration; it is extensively metabolized by the liver via CYP1A2 and CYP2E1 in processes that are capacity-limited.

Tinzaparin

Innohep® (POM)

Injection (single-dose syringe for SUBCUT use): tinzaparin sodium 20,000 units/mL: 8000 units (0.4mL syringe); 10,000 units (0.5mL syringe); 12,000 units (0.6mL syringe); 14,000 units (0.7mL syringe); 16,000 units (0.8mL syringe); 18,000 units (0.9mL syringe).

Injection (vial): tinzaparin sodium 20,000 units/2mL.

Injection (vial): tinzaparin sodium 40,000 units/2mL.

Generic (POM)

Injection (single-dose syringe for SUBCUT use): tinzaparin sodium 10,000 units/mL: 2500 units (0.25mL syringe); 3500 units (0.35mL syringe); 4500 units (0.45mL syringe).

Indications

- Treatment and prophylaxis of DVT and PE.
- Extended treatment of VTE and prevention of recurrences in adult patients with active cancer for 6 months.
- Other indications apply but are not normally relevant in palliative care; refer to the SmPC.

Contraindications and cautions

- Tinzaparin is contraindicated for use in:
  - acute gastroduodenal ulcer
  - body weight <40kg at the time of VTE (extended use only, due to lack of data)
  - cerebral haemorrhage (within 3 months, unless due to systemic emboli)
  - current or history of heparin-induced thrombocytopenia
  - haemorrhagic pericardial or pleural effusion; known haemorrhagic diathesis or other active haemorrhage
  - septic endocarditis.
- Use with caution in patients with an increased risk of bleeding complications:
  - brain tumours (increased risk of intracranial bleeding)
  - concurrent use of anticoagulant/antiplatelet agents/NSAIDs (see *Drug interactions*, p. 656)
  - diabetes mellitus (increased risk of hyperkalaemia and metabolic acidosis)
  - haemorrhagic stroke
  - hepatic impairment
  - renal impairment
  - retinopathy (hypertensive or diabetic)
  - surgery
  - trauma
  - thrombocytopenia
  - uncontrolled hypertension.

- A baseline platelet count should be taken prior to initiating treatment and monitored closely during the first 3 weeks (e.g. every 2–4 days) and regularly thereafter.
- Tinzaparin must not be administered by IM injection—risk of injection site haematoma.
- Advice should be sought from anaesthetic colleagues if considering an epidural intervention in a patient receiving tinzaparin, due to the risk of spinal haematoma.
- LMWH can inhibit aldosterone secretion, which can cause reversible hyperkalaemia. Patients with pre-existing renal impairment are more at risk. K^+ should be measured in at-risk patients prior to starting LMWH and monitored regularly thereafter, especially if treatment is prolonged beyond 7 days.
- *Tinzaparin should not be used to prevent valve thrombosis in patients with prosthetic heart valves, due to lack of data.*

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: anaemia; haematoma; haemorrhage; injection site reaction (nodule; pain; pruritus; subcutaneous haematoma at injection site; bleeding (from any site).
- *Uncommon*: bruising; dermatitis; ecchymosis; increased hepatic enzyme; hypersensitivity; pruritus; rash; thrombocytopenia.
- *Rare*: anaphylactic reactions; angioedema; hyperkalaemia; immunologically mediated heparin-induced thrombocytopenia; osteoporosis (long-term treatment); priapism; skin necrosis; thrombocytosis; toxic skin eruption (including Stevens–Johnson syndrome); urticaria.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None recognized.

Pharmacodynamic

- Drugs with anticoagulant or antiplatelet effect may enhance the effect of tinzaparin:
  - *aspirin*
  - *clopidogrel*
  - *dipyridamole*
  - *NSAIDs*.
- *ACE-Is*—increased risk of hyperkalaemia.
- *Amiloride*—increased risk of hyperkalaemia.
- *Antihistamines*—possibly reduce anticoagulant effect.
- *Ascorbic acid*—possibly reduces anticoagulant effect.
- *Corticosteroids*—increased risk of GI bleeding.
- *Spironolactone*—increased risk of hyperkalaemia.
- *SSRIs*—increased risk of bleeding.

Dose

Refer to Haematology for advice if platelets are below 75 × 10^9/L or bodyweight <40kg or >150kg.

Treatment of DVT and PE

- Usual dose 175 units/kg SUBCUT OD.
- Patients usually start oral anticoagulation at the same time and continue both until the INR is within the target range. This generally takes 6 days. However, cancer patients unsuitable for oral anticoagulation may require long-term treatment with LMWH. The benefit of long-term treatment should be assessed after 6 months; treatment is occasionally continued indefinitely.

Prophylaxis of DVT and PE

- For patients with very low or very high body weight, 50 units/kg SUBCUT OD may be considered as an alternative to the fixed dosing schedules below. For surgical patients, the first dose is given SUBCUT 2 hours before surgery. Administration should continue OD for as long as the patient is at risk of VTE.
- For medical prophylaxis (including immobile cancer patients), 4500 units SUBCUT OD. The duration of treatment depends upon the risk factors identified (e.g. immobile inpatients may be considered for treatment from admission until discharge).
- For surgical prophylaxis:
  - low to moderate risk—3500 units SUBCUT 2 hours before the procedure and for as long as the patient is at risk of VTE (e.g. for 7–10 days or longer until mobilized)
  - high risk—4500 units SUBCUT 12 hours before the procedure and for as long as the patient is at risk of VTE (e.g. for 7–10 days or longer until mobilized).
- †Long-distance air travel:
  - cancer patients are at risk of developing VTE during long-distance air travel (considered >6 hours)
  - supply the patient with sufficient quantities to cover flights and provide a cover letter for immigration purposes (see Chapter 2, *Travelling abroad with medicines*, p. 39)
  - 4500 units SUBCUT 2–4 hours prior to the flight. Should there be long-distance connections, only administer another dose if the following flight is >24 hours after the previous dose (e.g. following a stopover).

Dose adjustments

Elderly

- Usual adult doses recommended.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. The manufacturer advises caution due to an increased risk of bleeding.

- Dosage adjustments in patients with renal impairment *must* be based on CrCl, *not* eGFR. In the case of significant renal impairment, defined as CrCl <30mL/min, the dose of tinzaparin should be adjusted based on anti-factor Xa activity. If the anti-factor Xa level is less or greater than the desired range, the dose of tinzaparin should be increased or reduced, respectively, and anti-factor Xa measurement should be repeated after 3–4 doses. This process should be repeated until the desired anti-factor Xa level is achieved. The SmPC states that no accumulation occurs with CrCl >20mL/min.

Additional information

- The 20,000 units/2mL vial should be discarded 14 days after first use.
- Do not use if cloudiness or a precipitate is observed. The injection may turn yellow during storage but is still suitable for use.
- Actual body weight and CrCl should be used for dose calculations.
- Measurement of anti-factor Xa levels, in conjunction with the local Haematology department, can help guide the dose of tinzaparin in difficult cases. Refer to local guidelines for target anti-factor Xa ranges.
- Warfarin may be unsuitable for cancer patients who may require long-term treatment with LMWH. Treatment is occasionally continued indefinitely. Tinzaparin is currently unlicensed for extended treatment for up to 6 months in cancer patients.
- If switching from tinzaparin to warfarin, patients must continue both until the INR is within the target range. This generally takes 5 days.
- When switching from tinzaparin to a DOAC, the DOAC should be given 0–2 hours before the time that the next scheduled administration of tinzaparin would be due.
- When switching from a DOAC, the first dose of tinzaparin should be given at the time the next DOAC dose would be taken.
- The risk of heparin-induced thrombocytopenia is low with tinzaparin but may occur between the 5th and 21st day following initiation. If there is 30–50% reduction in the platelet count, LMWH should be stopped.

⊰ Pharmacology

Tinzaparin is an LMWH which acts mainly through its potentiation of inhibition of factor Xa and thrombin by antithrombin. It is eliminated primarily via the kidneys, hence the need for close monitoring in renal impairment. Local protocols may help to indicate when treatment of palliative care patients with tinzaparin is appropriate.

Tolterodine ♀

Standard-release

Detrusitol® (POM)
Tablet: 1mg (56); 2mg (56).

Generic (POM)
Tablet: 1mg (56); 2mg (56).

Modified-release

Detrusitol® XL (POM)
Capsule: 4mg (28).

Generic (POM)
Capsule: 2mg (28); 4mg (28).

Indications

- Urinary frequency.
- Urinary incontinence.

Contraindications and cautions

- Tolterodine is contraindicated for use in patients with:
  - myasthenia gravis
  - narrow-angle glaucoma
  - severe ulcerative colitis
  - toxic megacolon
  - urinary retention.
- There is a *possible* risk of QT prolongation/TdP. The SmPC advises the following:
  - do not prescribe for patients taking drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 660)
  - do not prescribe for patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - avoid concomitant use with other drugs known to inhibit CYP3A4 (see ➔ *Drug interactions*, p. 660).
- It should be used with caution in the following:
  - autonomic neuropathy
  - cardiac arrhythmia
  - congestive heart failure
  - the elderly (see ➔ *Dose adjustments*, p. 661)
  - GI reflux disease
  - hepatic impairment (see ➔ *Dose adjustments*, p. 661)
  - hiatus hernia
  - hyperthyroidism
  - prostatic hypertrophy
  - pyrexia (reduces sweating)
  - renal impairment (see ➔ *Dose adjustments*, p. 661).

- Tolterodine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: dry mouth, headache.
- *Common*: bronchitis, constipation, diarrhoea (overflow), dizziness, drowsiness, dyspepsia, fatigue, palpitations, paraesthesia, urinary retention, visual disturbances, vertigo.
- *Uncommon*: gastro-oesophageal reflux, memory impairment, tachycardia.
- *Unknown*: confusion, hallucinations.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Tolterodine is metabolized by CYP3A4 and CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- Co-administration with CYP3A4 inhibitors (see ➔ *Inhibitors* on the inside back cover) can cause increased pharmacological effect due to increased serum concentrations of the parent drug and active metabolite. This is likely to be of importance in poor CYP2D6 metabolizers or those co-prescribed both CYP3A4 and CYP2D6 inhibitors.
- The effect of grapefruit juice on the bioavailability of tolterodine is unknown.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *Donepezil*—effect may be antagonized.
- *β_2-agonists*—increased risk of tachycardia.
- *Cyclizine*—increased risk of anticholinergic adverse effects.
- *Domperidone*—may inhibit the prokinetic effect.
- *Galantamine*—effect may be antagonized.
- *Metoclopramide*—may inhibit the prokinetic effect.
- *Nefopam*—increased risk of anticholinergic adverse effects.
- *Rivastigmine*—effect may be antagonized.
- *TCAs*—increased risk of anticholinergic adverse effects.

Dose

Standard-release

- Initial dose 2mg PO BD; if adverse effects are troublesome, reduce dose to 1mg PO BD.

Modified-release

- Initial dose 4mg PO OD; revert to standard-release, should adverse effects become troublesome.

Dose adjustments

Elderly

- No dose adjustments are necessary.

Hepatic/renal impairment

- The manufacturer recommends that a dose of 1mg PO BD should be used initially for patients with hepatic or renal impairment (eGFR <30mL/min) using standard-release preparations.
- The modified-release formulation is not appropriate for use in patients with renal impairment (eGFR <30mL/min) but may be used at a dose of 2mg PO OD in hepatic impairment.

Additional information

- Standard-release tablets can be crushed and dispersed in water immediately prior to administration if necessary.
- A response to treatment should be seen within 4 weeks.

Pharmacology

Tolterodine is a competitive muscarinic receptor antagonist with selectivity for the bladder. It is metabolized by both CYP3A4 and CYP2D6; metabolism by CYP2D6 produces a metabolite with activity similar to the parent drug, which must be borne in mind should a CYP3A4 inhibitor be administered concurrently (see *Drug interactions*, p. 660).

Tramadol ♀

Standard-release (*CD3 POM*)

Zydol®
Capsule: 50mg (30; 100).
Soluble tablet: 50mg (20; 100).
Injection: 100mg/2mL (5).

Generic
Capsule: 50mg (30; 100).
Orodispersible tablet: 50mg (60) (*Zamadol® Melt*).
Oral drops: tramadol 100mg/mL (10mL).
Injection: 100mg/2mL (5).

Modified-release (*CD3 POM*)

Zydol® SR
Tablet (12-hour): 50mg (60); 100mg (60); 150mg (60); 200mg (60).

Generic
Tablet: 100mg (60); 150mg (60); 200mg (60).
Capsule: 50mg (60); 100mg (60); 150mg (60); 200mg (60).

Zydol® XL
Tablet (24-hour): 150mg (30); 200mg (30); 300mg (30) 400mg (30).

Generic
Tablet (24-hour): 100mg (30); 150mg (30); 200mg (30); 300mg (30); 400mg (30).

Combination with paracetamol

Tramacet® (CD3 POM)
Tablet: tramadol 37.5mg, paracetamol 325mg (60).
Effervescent tablet: tramadol 37.5mg, paracetamol 325mg (60).

Generic (CD3 POM)
Tablet: tramadol 37.5mg, paracetamol 325mg (60); tramadol 75mg, paracetamol 650mg (30).

Indications

- Moderate to severe pain.

Contraindications and cautions

- Do not use with a MAOI or within 14 days of stopping one (see ➔ *Drug interactions*, p. 665).
- Despite the *CredibleMeds® possible* risk of dose-related QT prolongation/TdP with tramadol, there are no such warnings in the UK SmPC. This is believed to be dose-related, linked to high plasma levels, and has been reported in renal failure. As such:
  - use cautiously with drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 665)

  - avoid concomitant administration of drugs that impair elimination (see ➔ *Drug interactions*, p. 665)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- Tramadol should be used cautiously with other drugs that display serotonergic effects (see ➔ *Drug interactions*, p. 665). There is a risk of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) when tramadol is used concomitantly with other serotonergic drugs (a small number of case reports). Treatment must be reviewed urgently if symptoms develop, tramadol should be discontinued if appropriate, and supportive symptomatic treatment should be initiated.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of tramadol and benzodiazepines (or *zopiclone*/*zolpidem*) increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution in epilepsy. There have been a number of case reports describing seizures at therapeutic doses. Tramadol should be used cautiously with other drugs that reduce the seizure threshold (see ➔ *Drug interactions*, p. 665).
- In addition, use with caution in patients with:
  - head injury
  - increased intracranial pressure
  - porphyria
  - severe impairment of liver and renal function (see ➔ *Dose adjustments*, p. 667)
  - sleep apnoea (respiratory effects of opioids are more pronounced during sleep).
- Tramadol has been linked to cases of altered glucose homeostasis, with hypoglycaemia being reported more frequently (a similar effect occurs with methadone).
- A withdrawal syndrome may occur with abrupt discontinuation; symptoms include agitation, anxiety, diarrhoea, hallucinations, insomnia, nausea, pain, sweating, and tremor.
- Phenylketonuria—*Zamadol*® orodispersible tablets contain aspartame, a source of phenylalanine.

- Tramadol is metabolized by CYP2D6 into its active metabolite M1. Ultrarapid metabolizers convert tramadol into M1 more rapidly and completely than other people, which can result in higher-than-expected plasma M1 concentrations. Even at usual doses, ultrarapid metabolizers may experience symptoms of overdose such as extreme sleepiness, confusion, or shallow breathing.
- Poor metabolizers or those taking concurrent CYP2D6 inhibitors (see ➔ *Drug interactions*, p. 665) may derive little or no analgesic benefit from tramadol. Titration of an alternative opioid is recommended, rather than substitution to an equianalgesic dose.
- See Table 1.3 for more information.

- The SmPC warns that prolonged use (of tramadol) may lead to dependence.
- Tramadol may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Opioids have been shown to have a variety of effects on components of the immune system in both *in vitro* and animal models. The clinical significance is presently unknown.
- Opioids are associated with a variety of endocrine effects through activity at the hypothalamic–pituitary–adrenal or hypothalamic–pituitary–gonadal axes. Clinical consequences of the resulting adrenal insufficiency and hypogonadism include anorexia, fatigue, hypotension, and sexual dysfunction (e.g. amenorrhoea, loss of libido, impotence). These effects are associated with chronic exposure (i.e. >1 month).
- Patients can paradoxically develop hypersensitivity to painful stimuli with repeated administration of an opioid, termed opioid-induced hyperalgesia (OIH). Given the range of factors involved, each case will be unique (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51). In view of the multimodal pharmacology of tramadol, the propensity to cause this effect, compared to other opioids, is unknown (see ➔ Chapter 2, *Opioid-induced hyperalgesia and tolerance*, p. 51).

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: dizziness; drowsiness (Tramacet®); nausea.
- *Common*: constipation; drowsiness; dry mouth; fatigue; headache; hyperhidrosis; vomiting.
- *Uncommon*: diarrhoea; GI discomfort; postural hypotension (more likely with IV use); pruritus; rash; tachycardia (more likely with IV use); urticaria.
- *Rare*: anxiety; bradycardia; BP increases; blurred vision; bronchospasm; confusion; delirium; dyspnoea; dysuria; epileptiform convulsions; hallucinations; hypersensitivity; involuntary muscle contractions; miosis; mydriasis; nightmares; paraesthesia; respiratory depression; sleep disorder; syncope; tremor; urinary retention.
- *Unknown*: hyperalgesia; hypoglycaemia; tolerance (to analgesic effect).

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Tramadol is metabolized to the opioid (+) O-desmethyltramadol (see *Pharmacology*, p. 668) by CYP2D6; additional metabolism of tramadol to inactive metabolites occurs via CYP3A4, CYP2B6, UGT2B7, and UGT1A8.
- Co-administration with CYP2D6 inhibitors may alter the analgesic effect of tramadol.
  - *Paroxetine* has been shown to reduce the analgesic benefit of tramadol.
  - The efficacy of tramadol may be altered by other CYP2D6 inhibitors such as *duloxetine*, *fluoxetine*, *haloperidol*, and *levomepromazine*. The clinical implications of co-administration with these drugs are unknown; the prescriber should be aware of the potential for altered response (see *Pharmacodynamic*).
- *Carbamazepine* reduces the analgesic benefit of tramadol through induction of CYP3A4.
- The clinical significance of co-administration of inhibitors of CYP3A4 (see *Inhibitors* on the inside back cover) is presently unknown. The prescriber should be aware of the potential for interactions (increased opioid effect).

Pharmacodynamic

- Risk of serotonin syndrome with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see *Contraindications and cautions*, p. 662)
  - *serotonergic drugs*—e.g. *fentanyl*, *methadone*, *mirtazapine*, *SNRIs*, *SSRIs*, *trazodone*.
- Tramadol is associated with a possible risk of prolongation of the QT interval (with high plasma levels). There is a potential risk that co-administration with other drugs that prolong the QT interval (e.g. *amiodarone*, *ciprofloxacin*, *citalopram*, *clarithromycin*, *domperidone*, *erythromycin*, *fluconazole*, *haloperidol*, *methadone*, *quinine*) may result in ventricular arrhythmias (see *Contraindications and cautions*, p. 662).
- *Antipsychotics*—increased risk of seizures.
- *Benzodiazepines*—see *Contraindications and cautions*, p. 662.
- *CNS depressants*—risk of excessive sedation.
- *Gabapentin/pregabalin*—possible opioid-sparing effect, with consequential adverse effects such as respiratory depression and sedation, necessitating opioid dose review.
- *Ketamine*—there is a potential opioid-sparing effect with ketamine and the dose of tramadol may need reducing.
- *Levomepromazine*—may be an additive hypotensive effect.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).
- *SNRIs/SSRIs*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

- *Warfarin*—possible risk of increased INR in susceptible patients.
- *Zolpidem/zopiclone*—see ➔ *Contraindications and cautions*, p. 662.

Dose

- The literature suggests an equianalgesic ratio for PO tramadol:PO morphine of 5:1. In practice, a 10:1 conversion is recommended because the opioid analgesia derived from tramadol in the clinical situation is unknown, due to dependence upon CYP2D6 activity (see ➔ *Pharmacology*, p. 668).
- The prescriber has two options when faced with the need to commence a more potent opioid:
  - stop tramadol and either titrate the strong opioid using standard-release formulations (e.g. morphine 5mg to 10mg PO 4-hourly PRN) or convert to a modified-release formulation (using a ratio of PO tramadol:PO morphine of 10:1, e.g. tramadol 200mg PO BD to Zomorph® 20mg PO BD)
  - gradual cross-tapering, e.g. reduce tramadol dose while introducing standard-release morphine 2.5mg to 5mg 4-hourly PRN.

Oral

- Slow titration with modified-release formulations has been shown to improve tolerability. Standard-release formulations are generally not as well tolerated.

Modified-release

- *12 hourly* modified-release preparations: initial dose 50mg PO BD, increasing to 100mg PO BD several days later, with further dose increases up to a maximum of 200mg PO BD.
- *24 hourly* modified-release preparations: initial dose 100mg PO OD, increasing to 150mg PO OD several days later, with further dose increases up to a maximum of 400mg PO OD.

Standard-release

- Initial dose 50mg PO, followed by doses of 50mg to 100mg PO not more frequently than 4-hourly, titrating the dose according to pain severity. Maximum dose of 400mg PO daily.
- *NB—20 oral drops can be considered equivalent in therapeutic effect to 50mg of standard-release tramadol.*

Combination with paracetamol

- Initial dose two tablets. Additional doses can be taken as needed, not less than 6 hours apart. Total daily dose must not exceed eight tablets.

Subcutaneous

- Rarely administered via CSCI in the UK.
- [+]Initial dose 100mg via CSCI, diluted with NaCl or WFI.

Dose adjustments

Elderly

- Dose as for adults; slow titration advised.
- Patients over the age of 75 years may need a dose reduction.

Hepatic/renal impairment

- In severe hepatic impairment, avoid the modified-release formulation; the dose interval (of the standard-release formulation) should be increased to 12-hourly.
- If CrCl is <30mL/min, avoid the modified-release formulation; the dose interval (of the standard-release formulation) should be increased to 8- to 12-hourly.
- In patients with CrCl <10mL/min, tramadol may be considered under specialist advice at a dose of 50mg PO 8- to 12-hourly (of the standard-release formulation).
- Patients undergoing haemofiltration or haemodialysis will not require post-dialysis because tramadol is removed very slowly.

Additional information

- Combination of tramadol with strong opioids has suggested a synergistic effect, such that lower doses of the more potent opioid could be used.[2]
- *Zamadol® SR* capsules can be opened, and the pellets added to jam or yoghurt. Alternatively, the pellets can be deposited onto a spoon. The spoon and pellets should be taken into the mouth, followed by a drink of water to rinse the mouth of all pellets. The pellets must not be chewed or crushed.
- The oral drops should be diluted with water before administration, independent of meals.
- *Tramacet®* may be useful for patients taking concurrent antidepressants in order to reduce the incidence of adverse effects.
- *Tramacet®* contains 7.8mmol (or 179.4mg) sodium per dose.
- Tramadol is reportedly *chemically* and *physically* compatible with dexamethasone, glycopyrronium, haloperidol, hyoscine butylbromide, and ketorolac. Under stated conditions, tramadol is *physically* compatible with metoclopramide, midazolam, ondansetron, and ranitidine. Anecdotally, tramadol is *physically* compatible with glycopyrronium and levomepromazine (although be wary of interaction).[3]
- CYP2D6 poor metabolizers cannot produce (+) M1, whereas ultrarapid metabolizers may produce excessive amounts. Drug interactions can affect the metabolism of (+/−) tramadol via enzyme inhibition (CYP2D6) or induction (CYP3A4 only). The clinical consequences of genotype and drug interaction depend upon the type of pain being treated, as the monoaminergic and opioid effects both independently produce analgesia. Genetic variations lead to the possibility of a modified adverse effect profile and varied analgesic response with tramadol.

Pharmacology

Tramadol is a centrally acting analgesic with a unique and complex pharmacology. Analgesia is produced by synergistic interaction between two distinct pharmacological effects. Tramadol has a μ-opioid effect and also activates descending anti-nociceptive pathways in the spinal cord via inhibition of reuptake of serotonin and noradrenaline and via presynaptic release of serotonin.

Following oral administration, about 90% of a dose is absorbed, but first-pass metabolism means tramadol has a mean oral bioavailability of approximately 75%. Tramadol is available commercially as a racemate, consisting of the enantiomers (+) tramadol and (−) tramadol that have different pharmacological actions. Opioid and serotonergic actions are associated with (+) tramadol, whereas noradrenaline reuptake inhibition is associated with (−) tramadol. The only pharmacologically active metabolite (+) O-desmethyltramadol (or (+) M1) is produced by the polymorphic cytochrome CYP2D6. The opioid effect of (+/−) tramadol is mostly due to (+) M1. Additional metabolism of (+/−) tramadol and (+) M1 is catalysed by CYP3A4 and CYP2B6.

References

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.
2. Marinangeli F, Ciccozzi A, Aloisio L, *et al*. Improved cancer pain treatment using combined fentanyl-TTS and tramadol. *Pain Pract*. 2007;**7**(4):307–12.
3. Dickman A, Schneider J. *The Syringe Driver: Continuous Subcutaneous Infusions in Palliative Care*, 4th Edition. Oxford: Oxford University Press; 2016.

Tranexamic acid

Cyklokapron® (POM)
Tablet (scored): 500mg (60).
Injection: 500mg/5mL (10).

Generic (POM)
Tablet (scored): 500mg (60).
Injection: 500mg/5mL (5; 10).

Indications

- Short-term use for haemorrhage or risk of haemorrhage in increased fibrinolysis or fibrinogenolysis.
- Local fibrinolysis (e.g. associated with prostatectomy, bladder surgery, menorrhagia, epistaxis).
- †Bleeding from wounds (topical application).[1]

Contraindications and cautions

- Contraindications and cautions should be individually assessed when used for topical use.
- Tranexamic acid is contraindicated for use in patients with:
  - active thromboembolic disease
  - history of venous or arterial thrombosis
  - severe renal failure (risk of accumulation).
- Use with caution in the following:
  - disseminated intravascular coagulation
  - massive haematuria (risk of ureteric obstruction)
  - past history of thromboembolic disease; renal impairment (see ➔ *Dose adjustments*, p. 670).
- If appropriate, patients on long-term treatment should have regular eye examinations and LFTs. Patients who develop visual disturbances should be withdrawn from treatment.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Rare*: allergic skin reactions, colour vision disturbances, retinal/artery occlusion, thromboembolic events.
- *Very rare*: arterial or venous thrombosis, diarrhoea, hypersensitivity reactions, nausea, vomiting.

Drug interactions

Pharmacokinetic

- None recognized.

Pharmacodynamic

- Will counteract the effect of fibrinolytic drugs.

Dose

General fibrinolysis

- IV: 1000mg (or 15mg/kg) every 6–8 hours, to be administered at a rate not exceeding 100mg/min.

Local fibrinolysis

- PO: 1000mg to 1500mg BD to TDS. Alternatively, 15mg/kg to 25mg/kg BD to TDS.
- IV: 500mg to 1000mg BD to TDS, to be administered at a rate not exceeding 100mg/min, followed by (CIVI) 25mg/kg to 50mg/kg if required, with dose to be given over 24 hours.
- †There are anecdotal reports of administering tranexamic acid via CSCI, in exceptional circumstances.
  - 1500mg to 2000mg via CSCI, diluted with WFI if possible (use a 30mL syringe).

Epistaxis

- 1000mg TDS PO for 7 days.

†*Topical*

- 500mg to 1000mg (using injection, or crushed tablets if warranted) directly into wound via suitable dressing, and apply pressure. Review after 10–20 minutes.

Dose adjustments

Elderly

- Usual adult doses recommended.

Hepatic/renal impairment

- No specific guidance is available for patients with hepatic impairment. Use the lowest effective dose.
- For patients with SeCr of 120micromol/L to 249micromol/L, oral dose should not exceed 15mg/kg BD. For patients with SeCr of 250micromol/L to 500micromol/L, oral dose should not exceed 15mg/kg OD. The drug is contraindicated in patients with severe renal impairment.

Additional information

- Tablets can be crushed and/or dispersed in water immediately prior to use if necessary.

Pharmacology

Tranexamic acid is an antifibrinolytic drug that competitively inhibits the activation of plasminogen to plasmin.

Reference

1. Coker N, Higgins DJ. Tranexamic acid applied topically to achieve haemostasis. *Anaesthesia*. 2000;**55**(6):600–1.

Trazodone ♀

Molipaxin® (POM)
Capsule: 50mg (84), 100mg (56).
Tablet: 150mg (28).

Generic (POM)
Capsule: 50mg (84), 100mg (56).
Tablet: 150mg (28).
Liquid: 50mg/mL (120mL bottle).

Indications

- Anxiety.
- Depression.
- ⁺Agitation associated with dementia.[1–3]
- ⁺Insomnia.[4]

Contraindications and cautions

- The SmPC states that 'possible interactions' with *MAOIs* have been occasionally reported. As such, the use of a *MAOI* (including *rasagiline* or *selegiline*—although see ➔ *Additional information*, p. 675) with trazodone, or within 14 days of stopping the former, is not recommended. Similarly, the use of a MAOI within 7 days of stopping trazodone is also not recommended. Concomitant use with *linezolid* or *moclobemide* should occur with caution, with close observation and monitoring of BP and other symptoms of serotonin toxicity (see ➔ Chapter 1, *Serotonin toxicity*, p. 29) such as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination.
- Trazodone demonstrates potent dose-dependent inhibition of hERG (human ether-a-go-go related gene) K^+ channels, which correlates with prolongation of the QT interval; cases of QT interval prolongation have been reported with trazodone only very rarely and in association with other risk factors. Nonetheless, there is a *conditional* risk of dose-dependent QT prolongation/TdP:
  - avoid concomitant administration of drugs that prolong the QT interval (see ➔ *Drug interactions*, p. 673)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome
  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - use with caution in patients with significant bradycardia and in those with recent acute myocardial infarction or uncompensated heart failure
  - closely monitor the patient if drugs known to affect CYP3A4 are co-administered (see ➔ *Drug interactions*, p. 673).
- Serotonin toxicity has been reported in patients using trazodone (see ➔ Chapter 1, *Serotonin toxicity*, p. 29). Treatment should be reviewed immediately if this is suspected, trazodone should be discontinued if appropriate, and supportive symptomatic treatment should be initiated. If treatment with trazodone and other serotonergic drugs is clinically

warranted, close observation of the patient is advised (see *Drug interactions*, p. 673). Avoid sudden discontinuation in order to minimize the occurrence of withdrawal symptoms such as nausea, headache, and malaise.

- Use with caution in epilepsy (may reduce the seizure threshold). *SSRIs* are considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.
- Careful dosing and regular monitoring are recommended in patients with:
  - acute narrow-angle glaucoma (small risk of anticholinergic effect)
  - cardiac disease
  - diabetes (may alter glycaemic control)
  - hyperthyroidism
  - severe hepatic impairment (see *Dose adjustments*, p. 674)
  - prostate hypertrophy (small risk of anticholinergic effect)
  - severe renal impairment (see *Dose adjustments*, p. 674).
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- While not specified in the UK SmPC, at high doses, trazodone may increase the risk of haemorrhage by inhibition of platelet serotonin reuptake. Use with caution in patients with bleeding disorders or with concurrent use of other drugs carrying a similar risk (see *Drug interactions*, p. 673).
- Severe hepatic disorders with potentially fatal outcome have been reported with trazodone use.
- Although trazodone is not believed to have substantial effects on the muscarinic receptor (see *Adverse effects*, p. 673 and *Pharmacology*, p. 675), anticholinergic effects have been reported, with the elderly reportedly being more susceptible. The risk is believed to be less than that posed by TCAs. Subtle deficits in attention, memory, and reasoning may occur with therapeutic dosages of anticholinergic drugs without signs of obvious toxicity. These deficits have often been mistaken for symptoms of early dementia in elderly patients.
- Trazodone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to Chapter 2, *Drugs and driving*, p. 41 for further information.
- See Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.
- Warn the patient about the importance of reporting signs of infection such as sore throat and fever during initial treatment (risk of agranulocytosis).

Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency of adverse effects is not stated, but the following have been reported more commonly in clinical trials:

- blurred vision; confusion; constipation; diarrhoea; disorientation; dizziness; drowsiness; dry mouth; fatigue; headaches; hypertension; hypotension; malaise; nasal congestion; nausea; nervousness; syncope; tremor; vomiting; weight changes (decrease or increase).

Post-marketing reports of adverse effects are shown below. It is difficult to estimate the frequency, as such reports are voluntary:

- agitation; anxiety; arrhythmia; blood dyscrasias (including agranulocytosis, anaemia, and thrombocytopenia); congestive heart failure; diplopia; hallucinations; hepatobiliary disorders (e.g. cholestasis, raised liver enzymes); hypersalivation; hyponatraemia (SIADH); palpitations; postural hypotension (elderly at greater risk); priapism
- prolonged QT interval, TdP, and ventricular tachycardia have been reported at doses of 100mg/day or less.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Trazodone is significantly metabolized by CYP3A4; additional metabolism occurs via CYP2D6. It is a weak CYP2D6 inhibitor. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Carbamazepine*—may reduce the effect of trazodone due to CYP3A4 induction. The clinical significance of co-administration with other inducers of CYP3A4 is unknown. Increased doses of trazodone may be required.
- *Phenytoin*—possible risk of increased phenytoin toxicity (mechanism unknown).
- Avoid grapefruit juice, as it may increase the bioavailability of trazodone through inhibition of intestinal CYP3A4.

Pharmacodynamic

- Trazodone *may* cause dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *erythromycin*, *fluconazole*, *haloperidol*, *quinine*) may result in ventricular arrhythmias (see *Contraindications and cautions*, p. 671).
- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see *Contraindications and cautions*, p. 671)

  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SNRIs*, *SSRIs*, *TCAs*, *tapentadol*, *tramadol*.
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.
- *Antidiabetics*—impaired glycaemic control.
- *Antihypertensives*—may require a reduction in the dose of the antihypertensive drug.
- *Carbamazepine*—increased risk of hyponatraemia.
- *CNS depressants*—risk of excessive sedation.
- *Cyproheptadine*—may inhibit the effects of trazodone.
- *Diuretics*—increased risk of hyponatraemia.
- *NSAIDs*—increased risk of GI bleeding (potentially worse with aspirin and naproxen).
- *SNRIs*—increased risk of seizures (and serotonin toxicity).
- *SSRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).

Dose

Anxiety

- Initial dose 75mg PO ON, increasing as necessary to 300mg PO ON (or 150mg PO BD).

Depression

- Initial dose 150mg PO ON, increasing as necessary to a usual maximum of 300mg PO ON (or 150mg PO BD). Under specialist guidance, the dose may be increased to 600mg PO daily in divided doses.

†*Agitation associated with dementia*

- Initial dose 25mg to 50mg PO ON, increasing as necessary to a maximum of 150mg PO ON. Higher doses of up to 300mg PO ON may be used in exceptional cases.
- Alternatively, trazodone may be used on a PRN basis to supplement regular medication for this condition (e.g. quetiapine). A suggested regime is 25mg PO every hour PRN to a maximum dose of 150mg/24 hours. In exceptional cases, this may be increased to 300mg/24 hours.

†*Insomnia*

- Initial dose 25mg to 50mg PO ON, increasing as necessary to a usual maximum of 100mg PO ON. Lower doses seem to be more effective.

Dose adjustments

Elderly

- Age-related changes in hepatic metabolism can produce significantly higher plasma concentrations of trazodone. Dose reductions are recommended:
  - depression: 100mg PO ON or 50mg PO BD initially and increase as necessary and tolerated to a maximum dose of 300mg PO daily

- anxiety: 25mg to 50mg PO ON and increase as necessary to a maximum dose of 300mg PO daily
- insomnia: use normal doses, but be mindful of possible reduced metabolism
- agitation/delirium: use normal doses as stated.

Hepatic/renal impairment

- Trazodone is extensively metabolized by the liver and has been associated with hepatotoxicity. The SmPC recommends caution when prescribing for patients with hepatic impairment, particularly in cases of severe impairment. Periodic liver monitoring is suggested.
- No dose adjustments are necessary in mild to moderate renal impairment. The manufacturer advises caution when used in patients with severe renal impairment.

Additional information

- Onset of action for insomnia can be within 1–3 hours of the initial dose. Onset of action for depression usually occurs within 2–4 weeks.
- The sedative effect of trazodone may persist the following morning, particularly if the dose is too high.
- Adverse effects may be minimized by taking the dose with or after a meal.
- Presently, NICE guidance for the recognition and management of depression in adults with a chronic physical health problem[5] states that mirtazapine and trazodone may be used with caution in patients receiving *rasagiline* or *selegiline*.
- Interest has developed recently in the repurposing of trazodone for treating Alzheimer's disease, based on associations between slow-wave sleep, amyloid-β aggregation, and cognition.[6]

Pharmacology

Trazodone is a triazolopyridine-based antidepressant that is structurally and pharmacologically unrelated to other antidepressants. It blocks post-synaptic 5-HT_{2A} and 5-HT_{2C} receptors, and is a partial agonist of 5-HT_{1A} receptors. At higher doses, it selectively inhibits presynaptic serotonin re-uptake; it is a very weak inhibitor of noradrenaline reuptake. Trazodone also antagonizes α_1-adrenergic receptors and is a histamine H_1 receptor inverse agonist. It is stated to have no effect on muscarinic receptors, although it is believed to reduce the levels of acetylcholine, thus producing anticholinergic effects.

This unique pharmacology permits trazodone to act as two different drugs. At low doses (e.g. 25mg to 50mg ON), it behaves as a hypnotic/anxiolytic, which is explained by the effects on 5-HT_{1A}, 5-HT_{2A}, α_1-, and H_1 receptors. At higher doses (e.g. 150mg ON), trazodone has an effect on SERT, which, when combined with the other effects, permits trazodone to have antidepressant activity. Unlike other antidepressants such as SSRIs, due to 5-HT_{2A} and 5-HT_{2C} antagonism, trazodone is not associated with sexual dysfunction, insomnia, or anxiety.

It is well absorbed by mouth, and food delays, but enhances, the amount absorbed. Trazodone is metabolized by CYP3A4 to an active metabolite

(meta-chlorophenylpiperazine), which is further metabolized by CYP2D6 to an inactive compound. Elimination is almost exclusively by urinary excretion of metabolites.

References

1. Seitz DP, Adunuri N, Gill SS, *et al*. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev*. 2011;**2**:CD008191.
2. Ringman JM, Schneider L. Treatment options for agitation in dementia. *Curr Treat Options Neurol*. 2019;**21**(7):30.
3. Davies SJ, Burhan AM, Kim D, Gerretsen P, Graff-Guerrero A, Woo VL. Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. *J Psychopharmacol*. 2018;**32**(5):509–23.
4. Savarese M, Carnicelli M, Cardinali V. Subjective hypnotic efficacy of trazodone and mirtazapine in patients with chronic insomnia: a retrospective, comparative study. *Arch Ital Biol*. 2015;**153**(2–3):231–8.
5. National Institute for Health and Care Excellence. Depression in adults with a chronic physical health problem: recognition and management. NICE clinical guideline [CG91]. 2009. Available from: https://www.nice.org.uk/guidance/cg91. Accessed 16 July 2019.
6. La AL, Walsh CM, Neylan TC, *et al*. Long-term trazodone use and cognition: a potential therapeutic role for slow-wave sleep enhancers. *J Alzheimers Dis*. 2019;**67**(3):911–21.

Venlafaxine

Standard-release

Generic (POM)
Tablet: 37.5mg (56); 75mg (56).

Modified-release

Efexor® XL (POM)
Capsule: 75mg (28); 150mg (28); 225mg (28).

Generic (POM)
Capsule: 37.5mg (28); 75mg (28); 150mg (28); 225mg (28; 30).
Tablet: 37.5mg (30); 75mg (28; 30); 150mg (28; 30); 225mg (28; 30).

Indications

- Major depressive episodes.
- Generalized anxiety disorder.
- Social anxiety disorder.
- ✝Sweats.[1,2]

Contraindications and cautions

- Venlafaxine is contraindicated for use in patients with:
  - conditions associated with a high risk of cardiac arrhythmia
  - uncontrolled hypertension.
- Do not use with an irreversible MAOI (including *rasagiline* and *selegiline*) or within 14 days of stopping one; at least 7 days should be allowed after stopping venlafaxine before starting an irreversible MAOI.
- The combination with selective reversible MAOIs (e.g. *linezolid*, *moclobemide*) is not recommended, although the SmPC offers no specific advice. Note that in exceptional circumstances, under specialist guidance, *linezolid* may be given with venlafaxine, but the patient must be closely monitored for symptoms of serotonin toxicity.
- Serotonin toxicity has been reported in patients using venlafaxine (see Chapter 1, *Serotonin toxicity*, p. 29). Treatment should be reviewed immediately if this is suspected, venlafaxine should be discontinued if appropriate, and supportive symptomatic treatment should be initiated. If treatment with venlafaxine and other serotonergic drugs is clinically warranted, close observation of the patient is advised (see *Drug interactions*, p. 679).
- There is a *possible* risk of QT prolongation/TdP (most reports are associated with overdose or other risk factors). The SmPC recommends assessing the balance of risks and benefits before prescribing venlafaxine to patients at high risk of serious cardiac arrhythmia or QT prolongation:
  - avoid concomitant administration of drugs that prolong the QT interval (see *Drug interactions*, p. 679)
  - avoid in patients with known QT interval prolongation or congenital long QT syndrome

  - correct hypokalaemia or hypomagnesaemia before commencing treatment
  - caution should be exercised in patients with cardiac comorbidities.
- Use with caution in epilepsy, as there is limited experience (may rarely lower the seizure threshold). *SSRIs* are considered to be the antidepressants with the lowest risk of precipitating seizures for patients with stable epilepsy.
- In addition, use with caution in the following:
  - concomitant use of drugs that increase the risk of bleeding (see ➔ *Drug interactions*, p. 679)
  - diabetes (may alter glycaemic control—hypoglycaemia)
  - elderly (greater risk of hyponatraemia)
  - glaucoma (may cause mydriasis)
  - heart disease (monitor BP)
  - hepatic and renal impairment (see ➔ *Dose adjustments*, p. 680)
  - history of bleeding disorders.
- Akathisia/psychomotor restlessness may occur within the first few weeks of treatment (consider discontinuing).
- Depression is associated with an increased risk of suicidal thoughts, self-harm, and suicide, which persists until remission. Note that the risk of suicide may increase during initial treatment.
- May precipitate psychomotor restlessness, which usually appears during early treatment. The use of venlafaxine should be reviewed.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant. Hyponatraemia has been associated with all types of antidepressants, although it is reportedly more common with SSRIs.
- Venlafaxine may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.
- Abrupt discontinuation should be avoided due to the risk of withdrawal reactions, e.g. agitation, anxiety, diarrhoea, dizziness, fatigue, headache, hyperhidrosis, nausea and/or vomiting, sensory disturbances (including paraesthesia), sleep disturbances, and tremor. When stopping treatment, the dose should be reduced gradually over at least 1–2 weeks. See ➔ Chapter 2, *Discontinuing and/or switching antidepressants*, p. 74 for information about switching or stopping antidepressants.

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Very common*: constipation; dizziness; drowsiness; dry mouth; headache; hyperhidrosis (including night sweats); insomnia; nausea (especially at initiation, less common with modified-release preparations).
- *Common*: abnormal dreams; agitation; akathisia; decreased appetite; asthenia; confusion; depersonalization; diarrhoea; dysgeusia; dyspnoea; fatigue; hot flushes; hypertension; hypertonia; nervousness; palpitations; paraesthesia; pollakiuria; pruritus; pyrexia, rash; sexual dysfunction (anorgasmia, ejaculation disorder, erectile dysfunction, decreased libido, menorrhagia); tachycardia; tinnitus; tremor; urinary hesitation/

retention; vasodilation, visual disturbances (blurred vision, mydriasis); vomiting; weight changes (decrease/increase); yawning.
- *Uncommon*: apathy; balance disorder; bruxism; dyskinesia; hallucinations; hypomania; mania; myoclonus; photosensitivity, syncope; SIADH/hyponatraemia.
- *Rare*: serotonin syndrome (see ➔ *Drug interactions*).
- *Unknown*: abnormal bleeding; arthralgia; gynaecomastia; hepatitis; movement disorders; pancreatitis; psychomotor restlessness; serotonin syndrome (see ➔ *Drug interactions*); SIADH; Stevens–Johnson syndrome.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Venlafaxine is metabolized mainly by CYP2D6. Also metabolized by CYP3A4, which is important in CYP2D6 poor metabolizers. It is a weak inhibitor of CYP2D6. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Haloperidol*—increased risk of adverse effects from both drugs due to CYP2D6 inhibition (may be of more significance for venlafaxine in CYP2D6 poor metabolizers)
- The clinical significance of co-administration with inhibitors of CYP2D6 and/or CYP3A4 (see ➔ *Inhibitors* on the inside back cover) is unknown, but plasma concentrations of venlafaxine may increase. The prescriber should be aware of the potential for interactions and that dose adjustments may be necessary.
- Avoid grapefruit juice, as it may increase the bioavailability of haloperidol through inhibition of intestinal CYP3A4.

Pharmacodynamic

- Risk of serotonin toxicity with:
  - *linezolid*; *MAO-B selective inhibitors* (*rasagiline*, *selegiline*); *MAOIs*; *moclobemide* (see ➔ *Contraindications and cautions*, p. 677)
  - *serotonergic drugs*—e.g. *methadone*, *mirtazapine*, *SSRIs*, *tapentadol*, *TCAs*, *tramadol*, *trazodone*.
- Venlafaxine carries a *small* risk of dose-related prolongation of the QT interval. There is a potential risk that co-administration with other drugs that also prolong the QT interval (e.g. *amiodarone*, *amitriptyline*, *citalopram*, *domperidone*, *erythromycin*, *fluconazole*, *methadone*, *quinine*) may result in ventricular arrhythmias (see ➔ *Contraindications and cautions*, p. 677).
- Dry mouth may lead to reduced effect of buccal, orodispersible, and sublingual formulations (e.g. *Abstral®*, *Effentora®*, GTN).
- *Anticoagulants*—potential increased risk of bleeding.
- *Antidiabetics*—impaired glycaemic control.

- *CNS depressants*—additive sedative effect.
- *Cyproheptadine*—may inhibit the effects of venlafaxine.
- *Diuretics*—increased risk of hyponatraemia.
- *Mirtazapine*—increased risk of seizures (and serotonin toxicity).
- *Nefopam*—increased risk of seizures (and serotonin toxicity).
- *NSAIDs*—increased risk of bleeding (potentially worse with aspirin and naproxen).
- *SSRIs*—increased risk of seizures (and serotonin toxicity).
- *Tapentadol*—increased risk of seizures (and serotonin toxicity).
- *TCAs*—increased risk of seizures (and serotonin toxicity).
- *Tramadol*—increased risk of seizures (and serotonin toxicity).
- *Trazodone*—increased risk of seizures (and serotonin toxicity).

Dose

Depression

- Initial dose 37.5mg PO BD, increased if necessary after at least 3–4 weeks to 75mg PO BD. Dose may be increased further on specialist advice, if necessary, in steps of up to 75mg every 2–3 days to a maximum of 375mg PO daily.
- Alternatively, 75mg *modified-release* PO OD, increased if necessary after at least 2 weeks to 150mg *modified-release* PO OD. Dose can be increased to a maximum of 375mg *modified-release* PO OD.

Generalized anxiety disorder

- 75mg *modified-release* PO OD, increased if necessary to up to 225mg *modified-release* PO OD, and dose can be increased at intervals of at least 2 weeks.

Social anxiety disorder

- 75mg modified-release PO OD; there is no evidence of greater efficacy at higher doses; dose can be increased, if necessary, at intervals of at least 2 weeks to a maximum dose of 225mg *modified-release* OD.

+Sweats

- Initial dose 37.5mg PO OD. If necessary, increase after 7 days to 37.5mg PO BD (or 75mg *modified-release* PO OD). Review treatment after 2 weeks and discontinue if no improvement (withdraw over 1–2 weeks). Higher doses have been suggested but should be used with caution.

Dose adjustments

Elderly

- No dose adjustment is necessary; however, wherever possible, lower doses should be used. The elderly are more susceptible to adverse effects.

Hepatic/renal impairment

- In patients with moderate hepatic impairment, the dose should be reduced by 50%. Avoid in severe hepatic impairment since no information is available.

- In patients with moderate renal impairment (GFR 10–30mL/min), the dose should be reduced by 50%. Avoid in severe renal impairment (GFR <10mL/min) since no information is available.

Additional information

- Antidepressant therapeutic response is usually seen after 2–4 weeks of treatment.
- Withdrawal effects can be seen as early as a few hours after missing a dose. Ensure patients adhere to the dosing schedule.
- Venlafaxine may be preferable to gabapentin in the treatment of hot flushes associated with breast cancer.
- Standard-release tablets can be crushed and mixed with water for administration via an enteral tube.

Pharmacology

Venlafaxine is an SNRI. Like duloxetine, it inhibits the reuptake of both serotonin and noradrenaline, with a weaker action on the reuptake of dopamine. It has no action at muscarinic, H_1, or α_1-adrenergic receptors. It is metabolized to its active metabolite O-desmethylvenlafaxine by CYP2D6. The clinical significance of inhibition of CYP2D6, or use in poor metabolizers, is unknown. An additional pathway involves CYP3A4.

References

1. Irani J, Salomon L, Oba R, Bouchard P, Mottet N. Efficacy of venlafaxine, medroxyprogesterone acetate, and cyproterone acetate for the treatment of vasomotor hot flushes in men taking gonadotropin-releasing hormone analogues for prostate cancer: a double-blind, randomised trial. *Lancet Oncol*. 2010;**11**(2):147–54.
2. Bordeleau L, Pritchard KI, Loprinzi CL, *et al*. Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. *J Clin Oncol*. 2010;**28**(35):5147–52.

Warfarin

Generic (POM)

Tablet: 0.5mg (*white*—28); 1mg (*brown*—28); 3mg (*blue*—28); 5mg (*pink*—28).

Oral suspension (sugar-free): 1mg/mL (150mL).

Indications

- Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation.
- Prophylaxis after insertion of prosthetic heart valves.
- Prophylaxis and treatment of venous thrombosis and PE.
- Transient attacks of cerebral ischaemia.

Contraindications and cautions

- Warfarin is contraindicated for use in the following circumstances:
  - bacterial endocarditis; haemophilia; peptic ulcer; recent surgery (within 24 hours); severe hepatic impairment (use LMWH); severe renal impairment; uncontrolled hypertension.
- The INR must be measured daily or on alternate days initially and then at longer intervals, depending on response, but usually every 12 weeks.
- For instructions on the management of bleeding—see the current edition of the *BNF*.
- Use with caution in:
  - elderly patients; renal impairment; hepatic impairment (LMWH may be preferred).

☹ Adverse effects

Refer to the SmPC for a full list of adverse effects. The frequency is not defined, but reported adverse effects include:

- alopecia; diarrhoea; hepatic dysfunction; hypersensitivity; jaundice; skin necrosis; skin rashes; purple toes syndrome; unexplained drop in haematocrit.

If the following occur, the SmPC advises that warfarin must be discontinued:

- epistaxis; fever; haemothorax; nausea; pancreatitis; purpura; vomiting.

Drug interactions

There are many potential drug interactions with warfarin, but as the INR is regularly monitored, it is more important to take account of the introduction or discontinuation of concurrent medication. The list below contains only those interactions most likely to be relevant in palliative care. Changes in medical conditions, especially hepatic involvement, and marked changes in the diet are also a potential source of changes in warfarin levels.

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Warfarin is a substrate of CYP1A2, CYP2C9, and CYP2C19. Several interactions are listed below, but refer to ➔ *Cytochrome P450 tables* on the inside back cover for a list of drugs that may potentially affect warfarin.
- The following can enhance the effect of warfarin:
  - *alcohol (acute use)*; *amiodarone* (may take up to 2 weeks to develop); *cephalosporins*; *ciprofloxacin*; *cranberry juice*; *erythromycin*; *fluconazole*; *metronidazole*; *miconazole*; *mirtazapine*; *omeprazole*; *penicillins*; *trimethoprim*.
- The following can reduce the effect of warfarin:
  - *alcohol (chronic use)*; *carbamazepine*; *menadiol (vitamin K)*; *phenobarbital*; *rifampicin*; *St John's wort*; *sucralfate*.

Pharmacodynamic

- The following drugs increase the risk of bleeding:
  - *aspirin*; *corticosteroids*; *NSAIDs*; *SSRIs*.
- *Azathioprine*—anticoagulant effect may be inhibited.

Dose

Refer to local guidelines.

Rapid anticoagulation

- 10mg PO on day 1, then subsequent doses based on INR.

Less urgent cases

- Lower loading doses can be introduced over a period of 3–4 weeks.
- The daily dose is usually between 3mg and 9mg.

Dose adjustments

Elderly

- No dose reductions necessary. Titrate the dose individually.

Hepatic/renal impairment

- Avoid in severe liver disease, especially if the INR is already raised. LMWH may be preferred. In moderate hepatic impairment, more frequent monitoring will be required.
- Avoid in severe renal impairment; LMWH may be preferred.

Additional information

- The use of warfarin in palliative care needs to be balanced with the burden of monitoring and drug interactions. The use of LMWH or DOAC is often preferred.
- As other pre-existing conditions may have an effect on INR, monitoring may be needed more frequently than in otherwise healthy patients who are at risk of, or requiring treatment for, thrombosis.
- Recommended ranges of therapeutic anticoagulation are the following:
  - INR 2–2.5: prophylaxis of DVT, including surgery in high-risk patients
  - INR 2–3: prophylaxis in hip surgery and fractured femur operations, treatment of DVT and PE; prevention of VTE in myocardial infarction,

transient ischaemic attacks, mitral stenosis with embolism, and tissue prosthetic heart valves
- INR 3–4.5: recurrent DVT and PE; mechanical prosthetic heart valves; arterial disease, including myocardial infarction.

Pharmacology

Warfarin is one of the coumarin anticoagulants, which act by antagonizing the effects of vitamin K. The anticoagulant effects do not develop fully until 48–72 hours after dose initiation, so heparins should be given in addition during that period. Warfarin is metabolized by CYP2C9 and, to a lesser extent, by CYP1A2 and CYP2C19. As with other drugs with a narrow therapeutic margin, particular care must be taken when drug regimens are altered. An additional complication is the effect of genetic polymorphism on warfarin metabolism, although monitoring can normalize for this.

Zoledronic acid

Zometa® (POM)
Concentrate for IVI: 4mg/5mL.
Solution for IVI: 4mg/100mL.

Generic (POM)
Concentrate for IVI: 4mg/5mL.
Solution for IVI: 4mg/100mL; 5mg/100mL.

Indications

- Treatment of tumour-induced hypercalcaemia (corrected Ca^{2+} >3.0mmol/L).
- Prevention of skeletal-related events in patients with advanced malignancies involving bone.
- †Cancer-related bone pain.[1]
- Paget's disease (*not discussed*).
- Osteoporosis (*not discussed*).

Contraindications and cautions

- Avoid in patients with:
  - cardiac disease (avoid fluid overload)
  - renal impairment (see ➔ *Dose adjustments*, p. 687)
  - severe hepatic impairment (limited data available).
- Assess renal function and electrolytes (e.g. Ca^{2+}, Mg^{2+}) before each dose, and ensure adequate hydration (especially hypercalcaemia)—dehydration increases the risk of renal failure.
- Assess the need for calcium and vitamin D supplements in patients receiving zoledronic acid other than for hypercalcaemia.
- Consider dental examination before initiating therapy, due to the possibility of inducing osteonecrosis of the jaw (see ➔ *Adverse effects*).

Adverse effects

Osteonecrosis of the jaw is a potential complication of bisphosphonate therapy. It has been reported in cancer patients, many of whom had a pre-existing local infection or recent extraction. Cancer patients are more likely to be at risk of osteonecrosis as a result of their disease, cancer therapies, and blood dyscrasias. Dental examination is recommended for patients undergoing repeated infusions of zoledronic acid (and other bisphosphonates), and dental surgery should be avoided during this treatment period as healing may be delayed.

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported with bisphosphonate use. Time to onset varies from one day to several months after initiation of treatment, but symptoms should improve upon discontinuation. Some patients will develop the same symptoms upon subsequent treatment with zoledronic acid or another bisphosphonate.

Atypical femoral fractures have been reported with bisphosphonate therapy. Although a rare occurrence, during bisphosphonate treatment, patients should be advised to report any new thigh, hip, or groin pain.

Refer to the SmPC for a full list of adverse effects.

- *Very common*: hypophosphataemia.
- *Common*: anaemia; decreased appetite; arthralgia; increased blood creatinine and urea; bone pain; conjunctivitis; fever; flu-like syndrome; headache; hypocalcaemia; myalgia; nausea; renal impairment; vomiting.
- *Uncommon*: abdominal pain; acute renal failure; anaphylaxis; anxiety; asthenia; blurred vision; bronchoconstriction; chest pain; constipation; cough; diarrhoea; dizziness; dry mouth; dysgeusia; dyspepsia; dyspnoea; haematuria; hyperaesthesia; hyperhidrosis; hypersensitivity reaction; hypoaesthesia; hypokalaemia; hypomagnesaemia; leucopenia; muscle cramps; osteonecrosis of the jaw; paraesthesia; peripheral oedema; proteinuria; pruritus; rash; scleritis and orbital inflammation; site reactions (injection); sleep disturbance; somnolence; stomatitis; thrombocytopenia; tremor; urticaria; weight increase.
- *Rare*: angioneurotic oedema; arthritis; confusion; hyperkalaemia; hypernatraemia; interstitial lung disease; joint swelling; pancytopenia; uveitis.
- *Very rare*: convulsions; episcleritis; hypoaesthesia and tetany (secondary to hypocalcaemia); osteonecrosis of the external auditory canal.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- None known.

Pharmacodynamic

- *Aminoglycosides*—may have additive hypocalcaemic effect.
- *Diuretics*—increased risk of renal impairment.
- *NSAIDs*—increased risk of renal impairment.
- *Thalidomide*—increased risk of renal impairment (in treatment of multiple myeloma).

Dose

The concentrate must be diluted with 100mL of NaCl or GLU and given in no less than a 15-minute IVI.

Treatment of tumour-induced hypercalcaemia

- Ensure patients are well hydrated prior to, and following, administration of zoledronic acid.
- Serum Ca^{2+} ≥*3.0mmol/L*:
  - 4mg by IVI as a single dose.
- Serum Ca^{2+} ≤*3mmol/L*:
  - risk of *hypocalcaemia* with zoledronic acid
  - consider fluids ± *pamidronate* 30mg or *ibandronic acid* 2mg if the patient is symptomatic.
- [+]In patients who fail to respond to 4mg, or relapse with a week of treatment, a dose of 8mg by IVI may be given. This approach was associated with a 50% response rate in one study (n = 69), although

the median time to relapse may be 2 weeks.[2] This higher dose is also associated with a higher risk of renal impairment.[3]
- In cases of bisphosphonate resistance, denosumab may be considered.

Prevention of skeletal-related events
- 4mg by IVI every 3–4 weeks.
- Note that calcium 500mg and vitamin D 400 units should also be taken daily.

†Cancer-related bone pain
- Bisphosphonates (and *denosumab*) appear to be beneficial in delaying the onset of bone pain, rather than producing a direct analgesic effect. Other options are suggested for acute management of cancer-related bone pain.
- 4mg by IVI every 3–4 weeks.
- Note that calcium 500mg and vitamin D 400 units should also be taken daily.

Dose adjustments

Elderly
- No dose adjustments are necessary.

Hepatic/renal impairment
- The SmPC advises caution in severe hepatic impairment due to the lack of data in this population.
- Zoledronic acid is not metabolized, but excreted unchanged via the kidney. For this reason, dose adjustments are necessary in patients with renal impairment when used for prevention of skeletal-related events and bone pain (see Table 3.19). For hypercalcaemia:
  - avoid if SeCr is >400micromol/L, unless benefits outweigh the risks—seek specialist advice (*ibandronate* or *denosumab* may be preferred)
  - no dose adjustment is necessary if SeCr is <400micromol/L.

Table 3.19 Zoledronic acid for prevention of skeletal-related events and bone pain according to serum calcium

Baseline creatinine clearance (mL/min)	**Recommended dose (mg)** (in 100mL of NaCl or GLU over 15 minutes via IVI)	**Volume of concentrate (mL)**	**Volume of solution for infusion to remove (mL)** (replace with NaCl or GLU)
>60	4.0	5.0	–
50–60	3.5	4.4	12
40–49	3.3	4.1	18
30–39	3.0	3.8	25
<30	Not recommended in severe renal impairment		

Additional information

- Corrected serum Ca^{2+} = actual serum Ca^{2+} + [(40 − serum albumin g/L) × 0.02].
- In the treatment of hypercalcaemia, serum Ca^{2+} levels should not be measured until 5–7 days post-dose. Ca^{2+} levels start to fall after 48 hours, with a median time to normalization of 4 days and normalization in 90% of patients within 7 days. Seek specialist advice, should the corrected serum Ca^{2+} concentration not return to normal after 7–10 days; a second dose of zoledronic acid can be given 7–10 days after the initial dose in such patients.
- Zoledronic acid provides a longer duration of effect before relapse, compared to *pamidronate* (4 weeks vs 2.5 weeks).
- The onset of treatment effect for skeletal-related events is 2–3 months.

Pharmacology

Zoledronic acid is a bisphosphonate that inhibits osteoclast activity, which, in turn, reduces bone resorption and turnover. It is excreted unchanged by the kidney.

References

1. Porta-Sales J, Garzón-Rodríguez C, Llorens-Torromé S, Brunelli C, Pigni A, Caraceni A. Evidence on the analgesic role of bisphosphonates and denosumab in the treatment of pain due to bone metastases: a systematic review within the European Association for Palliative Care guidelines project. *Palliat Med*. 2017;**31**(1):5–25.
2. Major P, Lortholary A, Hon J, *et al*. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;**19**(2):558–67.
3. Saad F, Gleason DM, Murray R, *et al*. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst*. 2002;**94**(19):1458–68.

Zolpidem

Stilnoct® (CD4a POM)

Tablet: 5mg (28); 10mg (28).

Generic (CD4a POM)

Tablet: 5mg (28); 10mg (28).

Indications

- Short-term treatment of insomnia.

Contraindications and cautions

- Zolpidem is contraindicated for use in patients with:
  - myasthenia gravis
  - obstructive sleep apnoea
  - respiratory failure
  - severe hepatic insufficiency.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of zolpidem and opioids increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution in patients with hepatic impairment (see ➔ *Dose adjustments*, p. 690).
- Lower initial doses should be used in the elderly (see ➔ *Dose adjustments*, p. 690).
- Sleep walking and other associated behaviours have been reported with zolpidem and are usually related to concomitant use of alcohol and other CNS depressants or to doses above the recommended.
- Zolpidem treatment can lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration. Patients with a history of alcohol and/or drug abuse also have an increased risk. Withdrawal symptoms that can occur after prolonged treatment include anxiety, hallucinations, insomnia, mood changes, restlessness, sweating, and tremor.
- Zolpidem may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: abdominal pain; agitation; anterograde amnesia; back pain; depression; diarrhoea; dizziness; fatigue; hallucination; headache; insomnia; nausea; nightmare; respiratory tract infection (upper or lower); somnolence; vomiting.

- *Uncommon*: aggression; appetite disorder; attention disturbance; confusional state; elevated liver enzymes; euphoric mood; hyperhidrosis; irritability; muscle spasms; muscular weakness; myalgia; paraesthesia; pruritus; rash; restlessness; somnambulism; speech disorder; tremor; visual disturbances (e.g. blurred vision, diplopia).
- *Rare*: depressed level of consciousness; fall (predominantly in the elderly); gait disturbance; libido disorder; liver injury (hepatocellular, cholestatic, or mixed); urticaria.
- *Very rare*: delusion; dependence; respiratory depression; visual impairment.
- *Unknown*: abnormal behaviour; anger; angioneurotic oedema; drug tolerance; psychosis.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Is metabolized mainly by CYP3A4, with a minor pathway involving CYP1A2. Drug interactions via cytochrome inhibition may be additive. Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➲ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- The effect of grapefruit juice on the bioavailability of zolpidem is unknown.

Pharmacodynamic

- *Antidepressants*—rare interaction may cause excessive drowsiness and hallucinations.
- *CNS depressants*—additive sedative effect.
- *Opioids*—see ➲ *Contraindications and cautions*, p. 689.

Dose

- 10mg PO ON.
- Treatment should not exceed 4 weeks.

Dose adjustments

Elderly

- Initial dose 5mg PO ON. The dose may be increased to 10mg PO ON if necessary.

Hepatic/renal impairment

- Initial dose in hepatic impairment is 5mg PO ON. The dose can be cautiously increased to 10mg PO ON if necessary. Note that zolpidem is contraindicated for patients with severe hepatic impairment due to the risk it may contribute to encephalopathy.
- No specific guidance is available for patients with renal impairment.

Additional information

- The tablets can be crushed and dispersed in water immediately before use.

Pharmacology

Zolpidem is a short-acting non-benzodiazepine hypnotic drug that initiates and sustains sleep without affecting total rapid eye movement (REM) sleep. It interacts preferentially with the GABA receptor via the ω_1 receptor subtype, which leads to the sedative effects seen, but also to the lack of muscle-relaxant effects. It is extensively metabolized by CYP3A4, with additional metabolism involving CYP1A2. All metabolites are inactive and eliminated in the urine and faeces.

Reference

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.

Zopiclone

Zimovane LS® (POM)
Tablet: 3.75mg (28).

Zimovane® (POM)
Tablet (scored): 7.5mg (28).

Generic (POM)
Tablet: 3.75mg (28); 7.5mg (28).

Indications

- Short-term treatment of insomnia.

Contraindications and cautions

- Zopiclone is contraindicated for use in patients with:
  - myasthenia gravis
  - respiratory failure
  - severe sleep apnoea syndrome
  - severe hepatic insufficiency.
- Following a report of death by respiratory arrest with *clonazepam* and *methadone* among the implicated drugs, the MHRA issued a Drug Safety Alert about concurrent use of opioids and benzodiazepines.[1] The SmPC warns that concurrent use of zopiclone and opioids increases the risk of sedation, respiratory depression, coma, and death. Concurrent use should be reserved for patients for whom alternative treatment options are not possible; the lowest effective dose should be used (with cautious titration). Patients should be closely monitored for signs of respiratory depression and sedation. Patients (and carers) should be made aware of these symptoms.
- Use with caution in patients with hepatic and/or renal impairment (see ➔ *Dose adjustments*, p. 693).
- Lower initial doses should be used in the elderly (see ➔ *Dose adjustments*, p. 693).
- Zopiclone treatment can lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration. Patients with a history of alcohol and/or drug abuse also have an increased risk.
- If treatment is limited to 4 weeks or less, discontinuation of therapy should not cause a withdrawal reaction. However, some patients may benefit from a tapered reduction. Withdrawal symptoms that can occur after prolonged treatment include anxiety, hallucinations, insomnia, mood changes, restlessness, sweating, and tremor.
- Sleep walking and other associated behaviours have been reported with zopiclone and are usually related to concomitant use of alcohol and other CNS depressants or to doses above the recommended.
- Zopiclone may modify reactions and patients should be advised not to drive (or operate machinery) if affected. Refer to ➔ Chapter 2, *Drugs and driving*, p. 41 for further information.

Adverse effects

Refer to the SmPC for a full list of adverse effects.

- *Common*: dry mouth; dysgeusia; somnolence.
- *Uncommon*: agitation; dizziness; fatigue; headache; nausea; nightmare; vomiting.
- *Rare*: aggression; anterograde amnesia; confusional state; dyspnoea; fall (predominantly in the elderly); hallucination; irritability; libido disorder; pruritus; urticaria.
- *Very rare*: anaphylaxis; angioedema; mild to moderate LFT abnormalities.
- *Unknown*: abnormal behaviour; anger; ataxia; delusion; dependence; depressed mood; diplopia; dyspepsia; incoordination; light-headedness; muscular weakness; paraesthesia; respiratory depression; restlessness; somnambulism; withdrawal syndrome.

Drug interactions

Examples of potential interactions are shown below. Refer to individual drug SmPCs for further information.

Pharmacokinetic

- Zopiclone is metabolized by CYP3A4 (forming two metabolites—one is active) and CYP2C8 (to the inactive metabolite). Co-administration with drugs that are metabolized by, or affect the activity (induction or inhibition—see ➔ *Inducers* and *Inhibitors* on the inside back cover) of, these pathways may lead to clinically relevant drug interactions and the prescriber should be aware that dosage adjustments may be necessary, particularly of drugs with a narrow therapeutic index.
- *Erythromycin*—increases plasma concentration and effects of zopiclone.
- The effect of grapefruit juice on the bioavailability of zopiclone is unknown.

Pharmacodynamic

- Dry mouth may lead to reduced effect of buccal, orodispersible. and sublingual formulations (e.g. *Abstral*®, *Effentora*®, GTN).
- *CNS depressants*—additive sedative effect.
- *Opioids*—see ➔ *Contraindications and cautions*, p. 692.

Dose

- 7.5mg PO ON.
- Treatment should not exceed 4 weeks.

Dose adjustments

Elderly

- Initial dose 3.75mg PO ON. The dose may be increased to 7.5mg PO ON if necessary.

Hepatic/renal impairment

- Initial dose in hepatic impairment is 3.75mg PO ON. The dose can be cautiously increased to 7.5mg PO ON if necessary. Note that zopiclone is contraindicated for patients with severe hepatic impairment.
- Initial dose in renal impairment is 3.75mg PO ON. The dose can be increased to 7.5mg PO ON if necessary.

Chronic respiratory insufficiency

- Initial dose in chronic respiratory insufficiency is 3.75mg PO ON. The dose can be subsequently increased to 7.5mg PO ON if necessary.

Additional information

- The tablets can be crushed and dispersed in water immediately before use.

Pharmacology

Zopiclone is a non-benzodiazepine hypnotic agent that initiates and sustains sleep without affecting total REM sleep. It is unlikely to produce a hangover effect. Its pharmacological properties include hypnotic, sedative, anxiolytic, anticonvulsant, and muscle-relaxant actions (at higher doses). Zopiclone binds with high affinity to the benzodiazepine receptor, although it is believed to act at a different site to benzodiazepines. Zopiclone is extensively metabolized to two major metabolites—one active (N-oxide zopiclone) and one inactive (N-desmethyl zopiclone). It is a substrate of CYP3A4 and CYP2C8/9. Both metabolites are excreted via the kidneys.

Reference

1. Medicines and Healthcare products Regulatory Agency (MHRA). Drug safety update. Volume 13, issue 8; March 2020, p. 5.

Index

For the benefit of digital users, indexed terms that span two pages (e.g., 52–53) may, on occasion, appear on only one of those pages.

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