

Palliative Care

# Adult palliative care formulary

December 2008

# ADULT PALLIATIVE CARE FORMULARY

## DISCLAIMER

The document is intended to be used as a guideline and it is the responsibility of users to ensure that the information it contains is used correctly. This formulary reflects current Australian/Tasmanian palliative care practice.

Medicines information derived from this formulary should be checked by a medical doctor with appropriate experience before administering medication. Medication doses and regimes should be modified in response to the individual patient/client's clinical situation.

This formulary is not intended to be a definitive guide and reference should be made to the Australian Medicines Handbook, MIMS Prescribing and the PBS schedule of benefits for further prescribing information.

### **For information on this document:**

Denise Ray  
Project Officer, Primary Health - Palliative Care  
Community Health Services  
Department of Health and Human Services  
Ph 03 6220 2515

### **Compiled by:**

Dr Paul Dunne AM  
Medical Director  
Palliative Care Service  
Tasmania

### **Adapted from the**

### **Nurse Maude Palliative Care Formulary**

<http://www.marypotter.org.nz/PCH/handbook/index.php>

Written by:

Dr Roderick D MacLeod; Jane Vella-Brincat; Dr A.D. (Sandy) Macleod.

### **Reviewed and revised by:**

Angus Thompson  
Research Fellow  
Unit for Medication Outcomes Research and Education (UMORE)  
Tasmanian School of Pharmacy  
University of Tasmania  
HOBART 7001

# ADULT PALLIATIVE CARE FORMULARY

## INTRODUCTION

Welcome to the Tasmanian Palliative Care Formulary for Adults.

This formulary has been developed to provide information for those healthcare professionals involved in prescribing and caring for adult patients receiving palliative care. Children have their own very special needs and appropriate advice should be sought on the management of children who require palliative care.

The formulary is split into five main sections:

- Matching symptoms to medication;
- Medication monographs;
- Use of syringe drivers;
- Prescribing outside of license; and
- Drug interactions.

Within each monograph attention is drawn to the general recommendations for dose adjustments required in renal or hepatic impairment. More information may be required before prescribing; for example the product literature may provide detailed advice on the specific dose adjustment required for some drugs based on glomerular filtration rate (GFR).

In the rare situation that a patient receiving palliative care is pregnant or breast-feeding, special considerations will apply and appropriate advice should be sought.

We are grateful to colleagues in New Zealand whose Nurse Maude formulary we have used as the basis for our document. This has been reviewed and adapted for Tasmanian practice using a range of reference sources (including AMH, APF, MIMS Prescribing, Martindale and PCF3) to provide accurate and pragmatic information.

We hope you find this first edition of the formulary is useful in your clinical practice. It is planned to review this document at six-monthly intervals and for it to evolve to meet the needs of those who use it. Consequently, if you have any suggestions as to how the formulary can be improved in any way, please do not hesitate to let us know.

Primary Health - Palliative Care

Community Health Services

Department of Health and Human Services

GPO Box 125

HOBART 7001

**November 2008**

# Contents

INTRODUCTION.....	3
Contents.....	4
DRUGS BY SYMPTOM.....	8
Anxiety.....	8
Acute.....	8
Chronic.....	8
Ascites (malignant).....	8
Bleeding (haemorrhage).....	8
Candidiasis.....	8
Confusion (see delirium).....	8
Constipation.....	8
Softeners.....	8
Stimulants.....	8
Rectal.....	8
Convulsions (seizures).....	9
Delirium (confusion).....	9
Depression (Major Depressive Episode).....	9
Diarrhoea.....	9
Hiccough.....	9
Hypercalcaemia.....	9
Insomnia.....	9
Intestinal obstruction.....	10
Itch (pruritus).....	10
Mouth Care.....	10
General mouthcare.....	10
Mouthwashes.....	10
Saliva stimulants.....	10
Saliva substitutes.....	10
Oral anti-fungal agents.....	10
Nausea/Vomiting (also refer to Figure.1).....	11
Higher centre stimulation.....	11
Vomiting centre stimulation.....	11
Vagal and sympathetic afferent stimulation.....	11
Chemoreceptor trigger zone stimulation.....	11
Vestibular nerve stimulation.....	11
Pharyngeal Stimulation.....	11
Complicated/ resistant.....	12
Pain (also refer to Figure.2).....	12
Nociceptive (soft tissue).....	12
Bone pain (with radiotherapy).....	12
Neuropathic pain.....	12
Raised intracranial pressure pain.....	13
Liver capsule pain.....	13
Tenesmus (see constipation).....	13
Intestinal spasm.....	13
Bladder spasm.....	13
Respiratory symptoms.....	13
Cough.....	13
Dyspnoea (breathlessness).....	13
Excess secretions.....	13
Restlessness (Terminal) - see pain, delirium, sedation.....	13
Sedation.....	13

Sweating.....	14
Thrombosis.....	14
Twitching (myoclonic jerks).....	14
Ulcer prophylaxis (gastro-intestinal).....	14
Wound Care.....	14
Figure 1: Matching drugs to Nausea and Vomiting - a rational approach.....	15
Figure 2: Matching drugs to Pain - a rational approach.....	16
NOTES ON DRUG MONOGRAPHS.....	17
DRUG MONOGRAPHS.....	19
ALPRAZOLAM.....	19
AMITRIPTYLINE.....	21
BACLOFEN.....	23
BENZYLAMINE.....	25
BISACODYL.....	26
BUPRENORPHINE.....	28
Buprenorphine Patches – a guide to morphine doses for breakthrough analgesia.....	32
CARBAMAZEPINE.....	33
CELECOXIB.....	35
CHLORPROMAZINE.....	37
CHOLESTYRAMINE.....	39
CIMETIDINE.....	40
CITALOPRAM.....	42
CLONAZEPAM.....	43
CLONIDINE.....	45
CODEINE PHOSPHATE.....	47
CYCLIZINE.....	49
DEXAMETHASONE.....	50
DIAZEPAM.....	52
DICLOFENAC.....	54
DOCUSATE.....	56
DOMPERIDONE.....	57
ENOXAPARIN.....	58
ESOMEPRAZOLE.....	60
FENTANYL.....	62
Fentanyl Patches – a guide to morphine doses for breakthrough analgesia.....	67
FLECAINIDE.....	68
FLUCONAZOLE.....	70
FLUNITRAZEPAM.....	72
FLUOXETINE.....	74
FRUSEMIDE (FUROSEMIDE).....	76
GABAPENTIN.....	78
GLYCERINE (GLYCEROL).....	80
GLYCOPYRROLONIUM (GLYCOPYRROLATE).....	81
HALOPERIDOL.....	82
HEPARIN.....	84
HYDROGEN PEROXIDE.....	85
HYDROMORPHONE.....	86
HYOSCINE BUTYLBROMIDE.....	89
HYOSCINE HYDROBROMIDE.....	91
IBUPROFEN.....	92
KETAMINE.....	94
KETOCONAZOLE.....	96
KETOROLAC.....	98
LACTULOSE.....	100

LOPERAMIDE.....	102
LORAZEPAM .....	103
METHADONE .....	105
METHOTRIMEPRAZINE (LEVOMEPRMAZINE) .....	109
METHYLPHENIDATE .....	111
METOCLOPRAMIDE .....	113
METRONIDAZOLE.....	115
MEXILETINE.....	117
MICONAZOLE.....	118
MICROLAX®.....	119
MIDAZOLAM.....	120
MIRTAZAPINE.....	122
MORPHINE.....	124
NALOXONE.....	128
NAPROXEN.....	129
NIFEDIPINE .....	131
NITRAZEPAM.....	132
NORTRIPTYLINE.....	134
NYSTATIN.....	136
OCTREOTIDE .....	138
OLANZAPINE .....	140
OMEPRAZOLE .....	142
ONDANSETRON.....	144
OXYBUTYNIN.....	146
OXYCODONE.....	148
PAMIDRONATE DISODIUM.....	151
PANTOPRAZOLE.....	153
PARACETAMOL (ACETAMINOPHEN) .....	155
PHENOBARBITONE (PHENOBARBITAL).....	157
PHENYTOIN.....	159
POLYETHELENE GLYCOL LAXATIVES (e.g. MACROGOL 3350) .....	161
PREDNISONE / PREDNISOLONE.....	162
PREGABALIN .....	164
PROCHLORPERAZINE.....	166
PROMETHAZINE.....	168
RANITIDINE.....	170
RIFAMPICIN .....	172
RISPERIDONE.....	174
SALIVA REPLACEMENTS .....	177
SENNA.....	178
SODIUM BICARBONATE.....	179
SPIRONOLACTONE.....	181
SUFENTANIL .....	182
TEMAZEPAM.....	184
TRAMADOL.....	186
TRANEXAMIC ACID.....	188
VALPROATE SODIUM (SODIUM VALPROATE) .....	189
VENLAFAXINE.....	191
WARFARIN .....	193
ZOLEDRONIC ACID .....	195
ZOPICLONE.....	196
SYRINGE DRIVERS .....	198
Figure 3. Summary of compatibility data for two drug combinations in syringe drivers... 199	
DRUG INTERACTIONS.....	200

“OFF-LABEL” PRESCRIBING.....	203
Appendix I.....	204

# DRUGS BY SYMPTOM

## Anxiety

### Acute

[Alprazolam](#)  
[Lorazepam](#)  
[Clonazepam](#)  
[Diazepam](#)

### Chronic

[Fluoxetine](#)  
[Citalopram](#)  
[Mirtazapine](#)

## Ascites (malignant)

[Spironolactone](#)  
[Frusemide](#)

## Bleeding (haemorrhage)

[Tranexamic acid](#)

## Candidiasis

[Fluconazole](#)  
[Ketoconazole](#)  
[Miconazole](#)  
[Nystatin](#)

## Confusion (see delirium)

## Constipation

### Softeners

[Docusate](#)

### Stimulants

[Bisacodyl](#)  
[Senna](#)  
[Docusate](#)  
[Lactulose](#)  
[Polyethylene glycol-laxatives](#)

### Rectal

[Bisacodyl](#)  
[Glycerol](#)  
Micro-enema  
[Microlax®](#)  
Mineral oil enema  
Phosphate enema

## **Convulsions (seizures)**

[Diazepam](#)  
[Valproate sodium](#)  
[Carbamazepine](#)  
[Phenytoin](#)  
[Clonazepam](#)  
[Midazolam](#)  
[Phenobarbitone](#)  
[Gabapentin](#)

## **Delirium (confusion)**

[Haloperidol](#)  
[Risperidone](#)  
[Methotrimeprazine](#)

## **Depression (Major Depressive Episode)**

[Amitriptyline](#)  
[Mirtazapine](#)  
[Venlafaxine](#)  
[Citalopram](#)  
[Fluoxetine](#)  
[Nortriptyline](#)  
[Methylphenidate](#)

## **Diarrhoea**

[Codeine phosphate](#)  
[Loperamide](#)  
[Morphine](#)  
[Octreotide](#)

## **Hiccough**

[Dexamethasone](#)  
[Prednisone / prednisolone](#)  
[Haloperidol](#)  
[Methotrimeprazine](#)  
[Metoclopramide](#)  
Benzodiazepines  
[Nifedipine](#)  
[Baclofen](#)  
[Valproate sodium](#)  
Antacids

## **Hypercalcaemia**

[Pamidronate disodium](#)  
[Zoledronic acid](#)  
[Dexamethasone](#)  
[Prednisone / prednisolone](#)

## **Insomnia**

[Temazepam](#)  
[Zopiclone](#)

## Intestinal obstruction

[Morphine](#)  
[Hyoscine butylbromide](#)  
[Haloperidol](#)  
[Cyclizine](#)  
[Dexamethasone](#)  
[Prednisone / prednisolone](#)  
[Octreotide](#)

## Itch (pruritus)

[Promethazine](#)  
[Cholestyramine](#) (bile salt binding resin)  
[Ranitidine](#)  
[Cimetidine](#)  
[Diclofenac](#)  
Benzodiazepines  
[Dexamethasone](#)  
[Prednisone / prednisolone](#)  
[Rifampicin](#) (chronic cholestasis)  
[Ondansetron](#)

## Mouth Care

### General mouthcare

Sugar free gum  
Carbonated drinks  
Dark Grape juice (for active enzyme)  
Paw Paw nectar  
Papaya enzyme

### Mouthwashes

[Sodium bicarbonate](#) (cleansing)  
[Hydrogen peroxide](#) (cleansing)  
[Benzydamine](#) (analgesic)

### Saliva stimulants

Iced pineapple chunks  
Lime juice  
Chewing gum

### Saliva substitutes

Biotene Oralbalance®  
Aqua®  
Oralube®

### Oral anti-fungal agents

[Nystatin](#)  
[Miconazole](#)

## **Nausea/Vomiting (also refer to Figure.1)**

### **Higher centre stimulation**

*(emotion - fear/anxiety)*

[Lorazepam](#)

[Methotrimeprazine](#)

### **Vomiting centre stimulation**

*(radiotherapy to the head, raised intracranial pressure)*

[Dexamethasone](#)

[Haloperidol](#)

[Cyclizine](#)

[Promethazine](#)

### **Vagal and sympathetic afferent stimulation**

*Hepatomegaly*

[Dexamethasone](#)

[Metoclopramide](#)

*Gastric stasis*

[Metoclopramide](#)

[Domperidone](#)

*Intestinal obstruction*

[Haloperidol](#)

[Dexamethasone](#)

[Hyoscine butylbromide](#)

[Cyclizine](#)

[Promethazine](#)

[Methotrimeprazine](#)

[Octreotide](#)

[Ondansetron](#)

### **Chemoreceptor trigger zone stimulation**

*(uraemia, hypercalcaemia, drugs e.g. morphine)*

[Haloperidol](#)

[Metoclopramide](#)

[Ondansetron](#)

### **Vestibular nerve stimulation**

*(motion)*

[Prochlorperazine](#)

[Haloperidol](#)

[Promethazine](#)

[Cyclizine](#)

[Hyoscine hydrobromide](#)

### **Pharyngeal Stimulation**

[Promethazine](#)

[Cyclizine](#)

[Hyoscine Hydrobromide](#)

### **Complicated/ resistant**

[Methotrimeprazine](#)

[Ondansetron](#)

### **Pain (also refer to Figure.2)**

#### **Nociceptive (soft tissue)**

[Paracetamol](#)

[Codeine phosphate](#)

[Diclofenac](#)

[Naproxen](#)

[Ibuprofen](#)

[Ketorolac](#)

[Celecoxib](#)

[Tramadol](#)

[Morphine](#)

[Methadone](#)

[Fentanyl](#)

[Buprenorphine](#)

[Ketamine](#)

[Hydromorphone](#)

[Oxycodone](#)

#### **Bone pain (with radiotherapy)**

[Paracetamol](#)

[Diclofenac](#)

[Naproxen](#)

[Ibuprofen](#)

[Ketorolac](#)

[Celecoxib](#)

[Morphine](#)

[Fentanyl](#)

[Buprenorphine](#)

[Pamidronate disodium](#)

[Zoledronic Acid](#)

#### **Neuropathic pain**

*Antidepressants*

[Nortriptyline](#)

[Amitriptyline](#)

[Fluoxetine](#)

[Citalopram](#)

*Anticonvulsants*

[Gabapentin](#)

[Pregabalin](#)

[Valproate sodium](#)

[Carbamazepine](#)

*Antiarrhythmics*

[Mexiletine](#)

[Flecainide](#)

Others

[Dexamethasone](#)

[Prednisone / prednisolone](#)

[Clonidine](#)

[Ketamine](#)

[Baclofen](#)

### **Raised intracranial pressure pain**

[Diclofenac](#)

[Morphine](#)

[Dexamethasone](#)

[Prednisone / prednisolone](#)

### **Liver capsule pain**

[Dexamethasone](#)

[Prednisone / prednisolone](#)

### **Tenesmus (see constipation)**

[Dexamethasone](#)

[Prednisone / prednisolone](#)

### **Intestinal spasm**

[Hyoscine butylbromide](#)

### **Bladder spasm**

[Oxybutynin](#)

[Hyoscine butylbromide](#) (high dose)

## **Respiratory symptoms**

### **Cough**

[Codeine phosphate](#)

[Morphine](#)

[Methadone](#)

### **Dyspnoea (breathlessness)**

[Morphine](#)

[Hydromorphone](#)

[Midazolam](#)

[Clonazepam](#)

[Dexamethasone](#)

[Prednisone / prednisolone](#)

### **Excess secretions**

[Glycopyrronium](#)

[Hyoscine hydrobromide](#)

## **Restlessness (Terminal) - see pain, delirium, sedation**

## **Sedation**

[Midazolam](#)

[Clonazepam](#)  
[Methotrimeprazine](#)  
[Phenobarbitone](#)

## **Sweating**

[Diclofenac](#)  
[Ranitidine](#)  
[Dexamethasone](#)  
[Prednisone / prednisolone](#)

## **Thrombosis**

[Enoxaparin](#)  
[Warfarin](#)

## **Twitching (myoclonic jerks)**

[Midazolam](#)  
[Clonazepam](#)  
[Phenobarbitone](#)

## **Ulcer prophylaxis (gastro-intestinal)**

[Omeprazole](#)  
[Esomeprazole](#)  
[Pantoprazole](#)  
[Ranitidine](#)

## **Wound Care**

[Metronidazole](#)

**Figure 1: Matching drugs to Nausea and Vomiting - a rational approach**

		Benzodiazepines - Lorazepam, Alprazolam	Chlorpromazine	Cyclizine	Dexamethasone	Domperidone	Haloperidol	Hyoscine hydrobromide	Hyoscine butylbromide (Buscopan)	Methotrimeprazine	Metoclopramide	Octreotide	Ondansetron	Promethazine (Phenergan)	Prochlorperazine
CTZ stimulation - chemotherapy			4*	3+	1+		1			3	2		1*	3	1
CTZ stimulation - medications, circulating toxins, radiotherapy to gut			4*	3	3+	3	1			3	2		1*	3	3*
Higher Centre stimulation: emotion, fear, anxiety		1								3					
VC stimulation - raised ICP, radiotherapy to head				2	1		1+	3*						2	
Vagal and Sympathetic afferent stimulation:	Hepatomegaly				1*						1				
	Gastric Stasis, commencement of opioids, constipation		4*			2	3				1			3*	2*
	Intestinal Obstruction			2	2+		1		2#			3	3#	3*	
Vestibular nerve stimulation - meniere's, labyrinthitis, base of skull				3			2	2*						2	1*
Pharyngeal stimulation		3		1				2*						1	
Refractory nausea and vomiting		<b>Refractory cases often have multiple causes requiring several drugs: seek specialist advice</b>								1				1	
<b>Legend:</b>		+ add to other first line medication													
1: Most effective, first line of therapy		* short term use only, due to side effect profile													
2: Second line therapy		# anti secretory, not anti nauseant													
3: Third line therapy		unlikely to help													
4: Rarely used, seek specialist advice		Abbreviations: CTZ = chemoreceptor trigger zone; VC = vomiting centre													

**Figure 2: Matching drugs to Pain - a rational approach**

	Superficial somatic	Deep somatic	Visceral	Neuropathic	Bone	Raised ICP	Liver capsule	Tenesmus	Bowel spasm	Bladder spasm	Uncontrolled	
Amitriptyline		3	3	2	3			3		2	3	<b>Legend:</b> 1 most effective, first line of therapy 2 add to 1. combination is effective 3 may be useful 4 may help, seek specialist advice unlikely to help, SE may be problem not indicated
Baclofen				4				4		3	4	
Buprenorphine		3	3	3	3		3	3	3	3		
Carbamazepine				4				4				
Celecoxib	I	I			I	2	2	3				
Citalopram			3	3				3		3		
Clonidine			4	4				4	4	4	4	
Codeine	3	3	I	3	3	3	3	3	2	3		
Dexamethasone		3	3	2	3	I	I		3		2	
Diclofenac	I	I			I	2	2	3				
Fentanyl		3	3	3	3	3	3	3	3	3	3	
Flecainide			4	4				4			4	
Fluoxetine	3		3	3				3				
Gabapentin				2				2			2	
Hydromorphone	3	3	I	3	3	3	3	3	2	3	3	
Hyoscine butylbromide			I						I	2		
Ibuprofen	I	I		3	I	2	2	3				
Ketamine			4	4				4			4	
Ketorolac	4	4		4	4	4	4	4			4	
Methadone			4	4	4	4	4	4	4	4	4	
Mexiletine			4	4				4			4	
Mirtazapine	3		3	3				3				
Morphine	3	3	I	3	3	3	3	3	2	3	3	
Naproxen	I	I		3	I	2	2	3			3	
Nortriptyline	3	3	3	2	3			3		2	3	
Oxybutynin			2						3	I		
Oxycodone	3	3	I	3	3	3	3	3	2	3	3	
Pamidronate		4			4							
Paracetamol	I	I	2	I	I	I	I	2	2	3	3	
Prednisone/Prednisolone		3	3	3	3	I	I		3		2	
Pregabalin				2								
Tramadol	2	2			2				2			
Valproate	3			2				2			3	
Venlafaxine	3		3	3				3				
Zoledronic acid		4			4							

**Note: drugs are listed in alphabetical order. They include examples from various drug classes. It is not advisable to use drugs from within one class together e.g. avoid using two NSAIDs**

# NOTES ON DRUG MONOGRAPHS

For drugs in this formulary, information to support prescribing is presented in monographs. The following notes on these monographs may be helpful to users:

## **Nomenclature**

Monographs are laid out in alphabetical order using the generic name in routine use in Australia. Where an alternative generic name may be in use, this is provided in parentheses and the most common brand names used in Australia are displayed in italics. For example:

### ***METHOTRIMEPRAZINE (LEVOMEPRMAZINE)***

*Nozinan*®

## **Contra-indications, cautions and special considerations**

In contrast to some other documents, contra-indications and cautions are displayed together in this formulary. In the Palliative Care environment strict contra-indications based on concerns about longer term toxicity may not necessarily apply. Where renal or hepatic disease may require a change in the use of the drug, this information is presented separately under the heading Special Considerations.

## **Interactions**

In this section, attention is drawn to those interactions that are considered most likely to occur and/or those which may have a more clinically significant outcome. It should be noted that patient factors such as pre-existing renal and hepatic function, the impact of disease state and genetic influences on drug handling will have a major influence on the occurrence of interactions. An individualised approach is essential, with prescribers remaining mindful that in the Palliative Care setting the priority is optimising symptom control for the patient.

Priority is given to highlighting interactions between drugs used in Palliative Care, therefore the information provided is **not** exhaustive. For example many of the macrolide antibiotics (e.g. erythromycin) and protease inhibitors (e.g. ritonavir) have profound effects on the metabolism of other drugs, but are not included in the monographs for the sake of brevity. Please refer to the Drug Interaction chapter of the formulary (page 214) and specific product literature for further guidance.

Interactions are presented systematically within each monograph. For example the interaction section of the monograph for Drug A will first describe interactions that impact on Drug A itself, followed by interactions where there is additive toxicity when Drug A is used in combination and finally the interactions where Drug A has an impact on other drugs.

### **Onset, peak and duration**

Information is provided, where available in the literature, on the typical time to onset of clinical effect, time to achieve peak clinical effect and duration of clinical effect. Where this information is not available, information on blood levels and half-lives is provided as an alternative. It should however be noted that due to the mechanism of action of some drugs, this surrogate information may not reliably reflect the clinical effects.

### **Availability**

The monographs list those formulations available to Australian patients. They provide information on the Pharmaceutical Benefits Scheme status of each formulation, in terms of the maximum quantity that can be prescribed, the maximum number of repeats and any restriction or authorisation requirements that apply. For example:

#### *Tablets*

500mg, PBS general benefit [100](0), PBS restricted benefit [200](3)<sup>1</sup>

PBS notes:

- I. Restricted benefit for patients with psychiatrist diagnosed OCD

i.e.

- Any patient may be issued with a prescription for 100 tablets without any repeats
- Prescriptions for 200 tablets with up to 3 repeats may only be issued to patients with psychiatrist diagnosed OCD

It should be noted that the Tasmanian Palliative Care Service has a limited budget to help with the provision of non PBS funded medicines to those clients who are registered with the service.

### **Opioid equivalents**

Within the monographs for some opioids, guidance is provided on suggested equivalence ratios when converting to alternative opioids. This guidance is based on the available literature and clinical experience within the Tasmanian and wider Australian Palliative Care community.

It should be noted that the response of individual patients to different opioids varies widely and the guidance should be modified by clinical judgement in all cases. As a general principle, it is often safer to start low and re-titrate with breakthrough doses, than to precipitate opioid toxicity.

# DRUG MONOGRAPHS

## ALPRAZOLAM

Alprax®, Kalma®, Xanax®, Zamhexal®

**Class:** Benzodiazepine – anxiolytic.

**Licensed indication:** anxiety including anxiety with symptoms of depression, panic.

**Recognised other use(s) in palliative care:** dyspnoea, agitation, restlessness, sleep disorders, muscle spasm.

**Contraindications/cautions:** proven allergy to alprazolam, avoid sudden withdrawal, needs careful titration in respiratory depression, Myasthenia Gravis.

**Specific considerations:**

*Hepatic impairment:* in mild-to-moderate hepatic impairment, use low doses of a short acting benzodiazepine to reduce the risk of precipitating coma. Contraindicated in severe hepatic impairment, especially when hepatic encephalopathy is present.

*Renal impairment:* use a lower initial dose in severe renal impairment due to an increased sensitivity to CNS depressant effects.

**Adverse reactions:**

*Common:* fatigue, drowsiness, light-headedness.

*Less common:* memory loss, hypersalivation, ataxia, slurred speech, respiratory depression, paradoxical excitation, euphoria, aggression and hostility.

**Interactions:**

Alprazolam is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of alprazolam may be increased by some cytochrome inhibitors: e.g. cimetidine, fluconazole, fluoxetine, ketoconazole, miconazole.

Concentration and effect of alprazolam may be decreased by some cytochrome inducers: e.g. carbamazepine.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

**Dosage:**

Anxiety:

*Oral:* initially 0.25-0.5mg 3 times daily, range 0.5-4mg per day in divided doses.

Panic disorder, dyspnoea:

*Oral:* initially 0.25-1mg 3 times daily, increasing by 0.25-1mg until symptoms are controlled; recommended maximum 10mg per day in divided doses.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** may enhance the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

**Onset:** of action in anxiety and panic around 10 to 20 minutes.

**Peak:** plasma levels occur 1 to 2 hours.

**Duration:** of effect not reported, however mean plasma half-life is 11-15 hours.

**Availability:**

*Tablets (scored):*

0.25mg, PBS authority benefit [50](5)

0.5mg, PBS authority benefit [50](5)

1mg, PBS authority benefit [50](5)

2mg PBS authority benefit [50](5)

Alprazolam preparations are available from a variety of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes: PBS authority benefit for Panic Disorder where other treatments have failed or are inappropriate.

**Notes:** See below for comparison with other benzodiazepines and zopiclone.

<b>Pharmacological properties and dose equivalents* for benzodiazepines and zopiclone</b>					
Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## AMITRIPTYLINE

Endep®

**Class:** Antidepressant – tricyclic (TCA).

**Licensed indications:** major depression, nocturnal enuresis.

**Recognised other use(s) in palliative care:** neuropathic pain.

**Contraindications/cautions:** proven allergy to amitriptyline or nortriptyline, arrhythmias, recent MI, use within 14 days of MAOI therapy or within 2 days of moclobemide therapy, epilepsy, urinary retention.

**Specific considerations:**

*Hepatic impairment:* halve the dose in severe hepatic impairment. Consider using an alternative tricyclic antidepressant for which serum concentrations can be measured, e.g. nortriptyline.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

*Common:* anticholinergic effects including dry mouth, blurred vision, urinary retention, drowsiness (tolerance may develop), constipation.

*Less common:* sweating, confusion (particularly in the elderly), arrhythmias, tachycardia, postural hypotension (may double the incidence of femoral fractures).

**Interactions:**

Amitriptyline is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of amitriptyline may be increased by some cytochrome inhibitors: e.g. cimetidine, fluconazole, fluoxetine, haloperidol, ketoconazole, methylphenidate, miconazole and valproate sodium.

Concentration and effect of amitriptyline may be decreased by some cytochrome inducers: e.g. carbamazepine, dexamethasone, phenobarbitone, rifampicin.

Absorption and effect of amitriptyline may be reduced by cholestyramine.

Additive effects with other anticholinergic drugs.

Additive effects with other drugs that prolong the QT interval, increasing the risk of arrhythmias.

Additive effects with other drugs that cause sedation.

Additive effects with other drugs that lower seizure threshold.

Use in combination with methylphenidate may cause hypertension.

**Dosage:**

Pain (neuropathic):

*Oral:* 10–50mg at night (start at 10mg in the elderly), maximum dose 75mg.

Depression:

*Oral:* 75–150mg at night (start at 25mg in the elderly), maximum dose 300mg.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:**

TCAs inhibit reuptake of noradrenaline and serotonin into pre-synaptic terminals. They also block cholinergic, histaminergic and  $\alpha_1$ -adrenergic receptors. The action of TCAs in pain is unclear but may be related to effects on serotonin and noradrenaline in the descending pain pathways.

**Onset:** of action in pain around 3 to 7 days, in depression around 14 to 21 days.

**Peak:** plasma levels occur after around 4 to 6 hours, however it should be noted that this bears no relation to the onset of the desired therapeutic effect.

**Duration:** of effect not reported, however half-life of amitriptyline is around 9 to 25 hours and that of the active metabolite (nortriptyline) around 15 to 39 hours.

**Availability:**

*Tablets*

10mg: PBS general benefit [50](2)

25mg: PBS general benefit [50](2)

50mg: PBS general benefit [50](2)

Currently only available as the Endep® brand.

**Notes:**

- May enhance effects of morphine and other opioids.
- Doses of > 75mg per day may be ineffective for neuropathic pain as there may be an analgesic “therapeutic window”.
- Metabolised to nortriptyline which may be better tolerated by some patients.

## **BACLOFEN**

*Baclo*®, *Clofen*®, *Lioresal*®, *Stelax*®

**Class:** Skeletal muscle relaxant.

**Licensed indications:** chronic spasticity associated with multiple sclerosis and spinal cord lesions, chronic spasticity of cerebral origin.

**Recognised other use(s) in palliative care:** neuropathic pain (third or fourth line).

**Contraindications/cautions:** proven allergy to baclofen, peptic ulceration, psychiatric disease, cerebrovascular disease, epilepsy, Parkinson's disease, diabetes.

### **Specific considerations:**

*Hepatic impairment:* use with caution, increased risk of adverse effects; monitor hepatic function.

*Renal impairment:* doses should be reduced.

### **Adverse reactions:**

*Common:* nausea, vomiting, constipation, diarrhoea, rash, hypotension, muscular weakness, myalgia, drowsiness, dizziness, headache, confusion, depression, hallucinations, ataxia, respiratory depression, visual disorders, urinary disorders

*Less common:* parasthesia, dyskinesia, paradoxical increase in spasticity, arrhythmia, dyspnoea, increased blood glucose, altered liver function tests.

**NOTE:** sudden cessation of baclofen may lead to a severe withdrawal syndrome; rhabdomyolysis, multiple organ failure and death has been reported with abrupt cessation of intrathecal baclofen.

### **Interactions:**

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Additive effects with other drugs that lower seizure threshold.

Additive effects with other drugs that cause hypotension.

Baclofen can affect blood glucose concentration, hypoglycaemic drugs should be prescribed with care.

### **Dosage:**

*Oral:* initially 5mg 3 times daily; increase by 15mg per day (in divided doses) every fourth day until therapeutic effect is reached; usual range 10-25 mg 3 times daily. Elderly, initially 5-10mg per day (in divided doses), increase by smaller increments and at longer intervals.

*Intrathecal:* not normally used, requires specialist input.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** unclear in pain, but may work through its effects on gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system and effects at the spinal level.

**Onset:** of action in spasm around 3 to 4 days, in pain uncertain (but if no benefit within 6 weeks it should be withdrawn slowly over 2 weeks).

**Peak:** plasma levels occur around 0.5 to 3 hours after oral dosing.

**Duration:** of effect not reported, however plasma half-life is around 3 to 4 hours.

### **Availability:**

*Tablets (scored and unscored):*

10 mg, PBS general benefit [100](5)

25 mg, PBS general benefit [100](5)

*Injection:*

0.05mg/mL 1 mL, under Section 100 provisions<sup>1</sup>

0.5mg/mL 20 mL, under Section 100 provisions<sup>1</sup>

2 mg/mL 5 mL, under Section 100 provisions<sup>1</sup>

Baclofen tablets are available from a range of manufacturers and these may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**PBS notes:**

Intrathecal injection available under Section 100 provisions: for severe chronic spasticity, where oral antispasmodic agents have failed or have caused unacceptable side effects, in patients with chronic spasticity of cerebral origin; or due to MS, spinal cord injury, or spinal cord disease.

**Notes:**

- none

## **BENZYDAMINE**

*Difflam Solution®*

**Class:** Non-steroidal anti-inflammatory drug (NSAID).

**Licensed indications:** painful conditions of mouth, throat.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to benzydamine, do not swallow, prolonged use.

**Specific considerations:**

*Hepatic impairment:* not applicable as not used systemically.

*Renal impairment:* not applicable as not used systemically.

**Adverse reactions:**

*Common:* no adverse effects reported commonly.

*Less common:* numbness or stinging sensation of the oral mucosa has been reported; hypersensitivity reactions including urticaria and bronchospasm may occur rarely.

**Interactions:** not applicable as not used systemically.

**Dosage:**

*Mouthwash:* 15mL gargled (for throat conditions) or swirled in mouth (for oral lesions) for 30 seconds every 1.5 to 3 hours as needed, expectorate after use, use undiluted unless stinging occurs.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** NSAID: inhibits the synthesis of prostaglandins through effect on cyclo-oxygenase.

**Onset:** of action usually within 15 minutes.

**Peak:** of action within 15 to 30 minutes.

**Duration:** of action up to 3 hours.

**Availability:**

*Mouthwash:*

0.15% 500mL, PBS restricted benefit [1](1)<sup>1</sup> Palliative Care authority [1](3)<sup>2</sup> [1](0)<sup>3</sup>

Currently only available as Difflam Solution®

PBS notes:

1. radiation induced mucositis (1 repeat).
2. initial supply (for up to 4 months) for palliative care patients where a painful mouth is a problem; continuing supply for palliative care patients where a painful mouth is a problem and where consultation with a palliative care specialist or service has occurred (3 repeats).
3. continuing supply for palliative care patients where a painful mouth is a problem (0 repeats).

**Notes:** none.

## **BISACODYL**

Dulcolax®, Bisalax®

**Class:** Laxative – stimulant.

**Licensed indications:** constipation.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to bisacodyl, acute abdominal pain, intestinal obstruction.

**Specific considerations:**

*Hepatic impairment:* absorption from GI tract minimal, unlikely to be relevant.

*Renal impairment:* absorption GI tract minimal, unlikely to be relevant.

**Adverse reactions:**

*Common:* abdominal cramps, diarrhoea, perianal irritation (usually with suppositories).

*Less common:* atonic colon (on prolonged use), hypokalaemia.

**Interactions:**

May antagonise effects of antispasmodics e.g. hyoscine butylbromide.

**Dosage:**

*Oral:* 5-10mg at night or twice a day.

*Rectal:* 10mg daily when required.

*Enema:* initially one micro-enema, then 1-2 tablets in the evening and 1 micro-enema in the morning for 3 days.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:**

Stimulates colonic activity via nerves in the intestinal mucosa mainly at the level of the colon. May also cause water and electrolyte accumulation in the gut lumen.

**Onset:** of action *Oral:* 6 to 12 hours; *Rectal:* 20 to 60 minutes; *Enema:* 5 to 15 minutes.

**Peak:** of action not applicable.

**Duration:** of action not applicable.

**Availability:**

*Tablets (enteric coated):*

5mg, PBS restricted benefit [200](2)<sup>1</sup>, Palliative Care authority [200](3)<sup>2</sup>[200](0)<sup>3</sup>

*Suppositories:*

5mg, Not PBS funded

10mg, PBS restricted benefit [30/36](5/4)<sup>1</sup> Palliative Care authority [30/36](3)<sup>2</sup>[30/36](0)<sup>3</sup>

*Enema:*

2mg/mL, 5mL, PBS restricted benefit, [25](2)<sup>1</sup>, Palliative Care authority [25](3)<sup>2</sup>

Bisacodyl preparations are available from a range of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function; patients who are receiving long term nursing care on account of age, infirmity or other condition in hospitals, nursing homes or residential facilities; for use by a patient who is receiving long term nursing care and in respect of whom a Carer Allowance is payable as a disabled adult; patients receiving palliative care; terminal malignant neoplasia; anorectal congenital abnormalities; megacolon.

2. Palliative Care Authority Benefit: initial supply (for up to 4 months) for palliative care patients where constipation is a problem and continuing supply where consultation with a palliative care specialist or service has occurred (3 repeats).
3. Palliative Care Authority Benefit: continuing supply for palliative care patients where constipation is a problem (no repeats).

**Notes:**

- may be useful in opioid induced constipation especially in combination with a softener.
- absorption from the gastrointestinal tract is minimal with enteric-coated tablets or suppositories.

## **BUPRENORPHINE**

Norspan®, Temgesic®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid (partial agonist).

**Licensed indications:** chronic severe disabling pain not responding to non-narcotic analgesics, opioid dependence.

**Recognised other use(s) in palliative care:** may have some benefit in combination with other opioids in the management of refractory neuropathic pain (specialist use).

**Contraindications/cautions:** proven allergy to buprenorphine, concomitant use with MAOIs or in patients who have received MAOIs within the previous two weeks.

Note: past nausea or hallucinations with opioids are not contraindications.

### **Specific considerations:**

*Hepatic impairment:* intensity and duration of action may be affected in patients with hepatic insufficiency, monitor carefully during treatment. Accumulation of buprenorphine may occur in those with severe hepatic impairment, alternative therapy should be considered.

*Renal impairment:* No special dose adjustment is necessary in patients with renal impairment.

### **Adverse reactions:**

Note: dermatological reactions to the adhesive in the patch do not preclude subsequent use of the oral or injectable form of the drug.

**The Tasmanian Palliative Care Service does not consider it is appropriate to initiate opioid therapy with buprenorphine patches in patients with cancer pain and advises that opioid naive patients should be titrated with quick release opioids until a steady state is reached and then converted to a patch.**

All opioids share a common range of adverse effects, although these are dose dependent and affected by circumstances of use. There is however significant variation between individuals in their response to different opioids and the different opioids have metabolites which may add to the adverse effects. Switching (rotating) to another, chemically distinct, opioid may therefore be useful to reduce adverse effects by allowing a wash out of these metabolites and presenting the mu receptors with a "fresh" opioid configuration.

**Common: Constipation occurs in up to 90% of patients on opioids, always ensure there is a bowel control plan with laxatives.** Nausea and vomiting are usually transient in the first few (1-5) days and may require metoclopramide or haloperidol to prevent symptoms. Transient confusion and sedation are also common, if persistent they will necessitate a reduction in the opioid dose or switching to another opioid. Dry mouth, dizziness and visual difficulty (particularly problems with accommodation) are also common.

*Less Common:* respiratory depression (usually only at high doses but does occur in the opioid naive when there is no titration of dosage, naloxone can reverse respiratory depression but will also reverse analgesia), myoclonic jerking, delirium, pruritus.

Respiratory depression is a serious side effect of opioids but is a symptom which is uncommon in Palliative Medicine where titration of opioids to pain or breathlessness is the norm. Respiratory rate reduction is often a late manifestation of opioid toxicity, but sedation is a better indicator and can be monitored by using a sedation score such as:

<b>Sedation Score</b>	
Score	Sedation level
0	wide awake
1	easy to rouse
2	easy to rouse, but cannot stay awake
3	difficult to rouse
With opioids, the aim is to keep sedation to a level of less than 2 on this scale.	

Adverse effects, including respiratory depression, may persist for longer when buprenorphine is given in the form of patches due to the depot effect (it takes about 12 hours after patch removal for the plasma concentration to drop by 50%) and where there has been accumulation e.g. due to hepatic impairment; extended monitoring may therefore be required.

Rare: visual hallucinations, hyperalgesia, biliary/urinary tract spasm, physical dependence (irrelevant in palliative care), SIADH, anaphylaxis, seizure.

### **Interactions:**

Buprenorphine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of buprenorphine may be increased by some cytochrome inhibitors e.g. ketoconazole.

Concentration and effect of buprenorphine may be decreased by some cytochrome inducers: e.g. carbamazepine, phenobarbitone, phenytoin and rifampicin.

Partial agonist effect of buprenorphine may reduce effect of opioid agonists.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

### **Dosage:**

*Sublingual:* 0.2-0.4mg every 6-8 hours.

*IM / IV:* 0.3-0.6mg every 6-8 hours.

Chronic Pain

*Patch:* specialist advice is recommended.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** partial agonist of the mu receptor, main area of activity in the descending pain pathways of the central nervous system.

**Onset:** of action *Sublingual:* 15 to 45 minutes; *IV:* 5 to 15 minutes; *IM:* 10 to 15 minutes; *Patch:* 12 to 24 hours.

**Peak:** of action *Sublingual:* 30 minutes to 3 hours; *IV:* 5 to 15 minutes; *IM:* 10 to 15 minutes; *Patch:* up to 72 hours.

**Duration:** of action *Sublingual:* 6 to 8 hours; *IV:* 6 to 8 hours; *IM:* 6 to 8 hours; *Patch:* 7 days.

### **Availability:**

*Tablets (sublingual):*

0.2mg, Not PBS funded.

*Injection:*

0.3mg/mL 1 mL, Not PBS funded.

*Transdermal patch:*

0.005mg/hour, PBS restricted benefit, [2](0) <sup>1</sup>

0.01mg/hour, PBS restricted benefit, [2](0) <sup>1</sup>

0.02mg/hour, PBS restricted benefit, [2](0)<sup>1</sup>

Buprenorphine sublingual tablets are currently only available as the brand Temgesic® and the patches only as the brand Norspan®.

PBS notes:

- I. Restricted PBS benefit for chronic severe disabling pain not responding to non-narcotic analgesics, no repeats

**Notes:**

- paracetamol and an NSAID are effective co-analgesics when given with opioids such as buprenorphine in the treatment of bone and soft tissue pain.
- the role of buprenorphine patches in Palliative Care is still being assessed.
- the manufacturer may recommend starting with the 0.005mg/hour patch in opioid naive patients, but the absorption and uptake of the medication through the skin is variable and toxicity could occur.
- the Tasmanian Palliative Care Service recommends that opioid naive patients should initially be titrated with a quick acting opioid until a steady state is attained and then switched to a patch of equivalent strength.
- it takes at least three days to achieve somewhere near a steady state and breakthrough analgesia will need to be prescribed in the interim. Once commenced, the patch can be gradually titrated upwards after 3 days to a maximum of 0.04mg/hour (2 x 0.02mg/hour patches).
- the absorption of buprenorphine from patches may be increased if the patient is febrile.
- the absorption of buprenorphine from patches will be increased if the application site is exposed to external heat sources such as electric blankets, heat pads, heat lamps, saunas etc; avoid such contact where possible.
- write the date and time of application on the patch with a permanent marker (or a ball point pen if a marker is not available).
- when applying the patch, it should be pressed firmly in place with the palm of the hand for 30 seconds.
- patches should not be applied after a hot bath or shower.
- patches should be applied to dry, hairless, non-irritated skin on the upper part of the body or upper arm.
- patch application sites should be rotated to reduce the risk of irritation.
- after removal, used patches should be folded so that the adhesive side of the patch adheres to itself, then wrapped and disposed of safely.
- each patch must be changed every 7 days.
- if sedation occurs the patch should be removed, however the sub-dermal depot of buprenorphine will remain active; the concentration decreases by around 50% every 12 hours.
- do not start an alternative long acting opioid for at least 24 to 48 hours after removing the last patch.
- buprenorphine transdermal patches are unsuitable for the management of acute pain because of the delayed onset and prolonged duration of action; rapid and safe dose titration in this setting is NOT possible.
- converting from oral morphine to transdermal buprenorphine (or vice-versa):
  - care is required due to the variation in response to different opioids between individuals and the variable rate of absorption from buprenorphine patches.

- one suggested equivalence ratio is transdermal buprenorphine : oral morphine = 100 : 1, for example transdermal buprenorphine 0.005mg/hr = oral morphine 12mg/24hr.
- morphine may be used for breakthrough analgesia for patients on transdermal buprenorphine, in this situation the following may serve as a useful guide to doses:

## Buprenorphine Patches – a guide to morphine doses for breakthrough analgesia

Buprenorphine patch strength	Buprenorphine delivery rate	24 hour oral morphine dose	*Oral morphine breakthrough dose	24 hour SC morphine dose	*SC morphine breakthrough dose
Buprenorphine 5 micrograms/hr (Norspan® 5) Note: each patch contains total of 5 mg buprenorphine	120 micrograms/24 hrs	9 - 13 mg/24 hrs	2.5 - 5 mg	4 - 6 mg/24 hrs	1 - 2 mg
Buprenorphine 10 micrograms/hr (Norspan® 10) Note: each patch contains total of 10 mg buprenorphine	240 micrograms/24 hrs	18 - 26 mg/24 hrs	5 - 10 mg	8 - 12 mg/24 hrs	2 - 4 mg
Buprenorphine 20 micrograms/hr (Norspan® 20) Note: each patch contains total of 20 mg buprenorphine	480 micrograms/24 hrs	36 - 53 mg/24 hrs	10 - 20 mg	16 - 24 mg/24 hrs	4 - 7.5 mg

\* Because buprenorphine is a partial agonist with high receptor binding affinity, it impairs access to the opioid receptors by other agonists such as morphine; therefore breakthrough morphine doses need to be higher than would be suggested by the standard 24 hour dose equivalence. **Please note that micrograms (rather than mg) are used as the units for buprenorphine release rates in this table.**

# **CARBAMAZEPINE**

Tegreto<sup>®</sup>, Teril<sup>®</sup>

**Class:** Anticonvulsant.

**Licensed indications:** epilepsy, including simple and complex partial seizures and generalised tonic-clonic seizures; trigeminal and glosso-pharyngeal neuralgias; acute mania and prevention of bipolar disorder.

**Recognised other use(s) in palliative care:** neuropathic pain.

**Contraindications/cautions:** proven allergy to carbamazepine, bone marrow depression.

**Specific considerations:**

*Hepatic impairment:* reduce dose or avoid use in severe hepatic impairment.

*Renal impairment:* caution advised by manufacturer.

**Adverse reactions:**

*Common:* dry mouth, diarrhoea, constipation, dizziness, nausea, ataxia (dose related), blurred vision, asymptomatic hyponatraemia and abnormal LFTs.

*Less common:* vomiting, confusion (dose related), blood dyscrasias, SIADH, hepatitis, Stevens-Johnson syndrome, Systemic Lupus Erythematosus.

**Interactions:**

**The clinical use of carbamazepine is complicated significantly by many drug interactions, it is therefore not a first line choice and should only be prescribed by those who are familiar with its use.**

Carbamazepine is metabolised by the Cytochrome P450 system and has a narrow therapeutic range. Further complexity is added as carbamazepine induces its own metabolism. There is therefore a high risk of clinically significant interactions when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of carbamazepine may be increased by some cytochrome inhibitors: e.g. cimetidine, fluconazole, fluoxetine, haloperidol, ketoconazole, metronidazole, miconazole, octreotide.

Various interactions have been reported when carbamazepine is given with other anticonvulsants that induce or inhibit the Cytochrome P450 system e.g. phenytoin, phenobarbitone and valproate.

Risperidone may increase levels and effect of carbamazepine.

Carbamazepine is also a potent inducer of some of the Cytochrome P450 enzymes involved in the metabolism of other drugs. Where these drugs have a narrow therapeutic range there is a high risk of clinically significant interactions:

Carbamazepine may induce the metabolism and decrease the concentration and effect of alprazolam, amitriptyline, buprenorphine, carbamazepine (auto-induction), clonazepam, dexamethasone, fentanyl, flecainide, haloperidol, methadone, midazolam, mirtazapine, nortriptyline, olanzapine, prednisolone, risperidone, tramadol, warfarin.

Additive effects with other serotonergic drugs, increasing risk of serotonin syndrome.

Additive effects with other hepatotoxic drugs, including paracetamol.

**Dosage:**

Pain (neuropathic):

*Oral:* Initially 100-200mg once or twice daily, titrate according to effect and tolerability; increasing by 100-200mg every 2 weeks to a maximum of 800-1200mg per day in two divided doses. Blood level monitoring may be useful, although some patients will achieve

beneficial effects on neuropathic pain from what are considered sub-therapeutic levels in epilepsy (see notes below).

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** in pain mechanism is still unknown, may be related to reduction in nerve cell excitability through preventing repetitive neuronal discharges by blocking the voltage-dependent and use-dependent sodium channels.

**Onset:** of action in pain is around 3 to 7 days.

**Peak:** of action not reported; however carbamazepine is absorbed slowly and irregularly from the gastrointestinal tract, with variable peaks; typically normal release tablets 4 to 5 hours; syrup 1.5 hours; controlled release tablets 3 to 12 hours.

**Duration:** of action not reported, however the half life of carbamazepine varies widely (partly due to auto-induction) but is usually in the range 5 to 26 hours, the half life of the active metabolite is also considered to be within this range.

**Availability:**

*Tablets (scored):*

100mg, PBS general benefit [200](2)

200mg, PBS general benefit [200](2)

*Tablets (controlled release, scored):*

200mg, PBS general benefit [200](2)

400mg, PBS general benefit [200](2)

*Oral liquid:*

20mg/mL, PBS general benefit [300ml](5)

Carbamazepine preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours or coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- co-analgesic often used with opioids in the treatment of neuropathic pain.
- monitor plasma concentrations.
- given the narrow therapeutic range of carbamazepine, it may be advisable to maintain patients on one brand as different brands may not be bio-equivalent.
- may be used in neuropathic pain where tricyclic antidepressants have failed or in combination with tricyclic antidepressants.
- gabapentin or pregabalin may be more effective anticonvulsants in neuropathic pain.
- normal therapeutic range for carbamazepine (in epilepsy) is 4–12 mg/L (or 17–50 micromol/L) measured as steady-state trough plasma concentration.

# CELECOXIB

Celebrex®

**Class:** Non-steroidal anti-inflammatory (NSAID) / COX-2 inhibitor.

**Licensed indications:** pain associated with inflammation in osteoarthritis and rheumatoid arthritis, pain from dysmenorrhoea.

**Recognised other use(s) in palliative care:** other pain associated with inflammation.

**Contraindications/cautions:** proven allergy to celecoxib, gastro-intestinal ulceration (although may be less than with standard NSAIDs), asthma (in NSAID sensitive patients), heart failure, sulphonamide allergy.

**Specific considerations:**

*Hepatic impairment:* doses of celecoxib should be reduced by 50% in patients with moderate hepatic impairment, contra-indicated in those with severe impairment.

*Renal impairment:* avoid if creatinine clearance less than 30mL/min.

**Adverse reactions:**

*Common:* diarrhoea, indigestion, nausea.

*Less common:* gastro-intestinal ulceration (more common in the elderly), dizziness, rash, nephrotoxicity, hepatitis, oedema, hypertension, headache, tinnitus.

**Interactions:**

Celecoxib is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

Additive effects with other nephrotoxic drugs.

Celecoxib may reduce the effect of diuretics and antihypertensives.

**Dosage:**

*Oral:* 100-200mg twice a day.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** inhibits prostaglandin synthesis via selective inhibition of COX-2 enzyme.

**Onset:** of action not reported.

**Peak:** of action not reported, however peak plasma concentrations occur after approximately 2 to 3 hours.

**Duration:** of action not reported, however plasma half-life is around 8 to 12 hours.

**Availability:**

*Capsules:*

100mg, PBS restricted benefit [60](3)<sup>1</sup>

200mg, PBS restricted benefit [30](3)<sup>1</sup>

Currently only available as the brand Celebrex®.

PBS notes:

1. restricted benefit for symptomatic treatment of osteoarthritis and rheumatoid arthritis.

**Notes:**

- unless contra-indicated, NSAIDs such as celecoxib should be given alongside regular full-dose paracetamol to provide optimal effect.

- NSAIDs (with paracetamol as above) are an effective co-analgesic when given with opioids in the treatment of bone and soft tissue pain.
- may cause less gastrointestinal toxicity than standard NSAIDs, but causes the same nephrotoxicity.
- the COX-2 sub-class of NSAIDs has been the subject of a number of drug withdrawals due to cardiovascular and other adverse effects, continued use requires caution and an appraisal of the likely risk and benefit.
- gastric cytoprotection with a proton pump inhibitor e.g. omeprazole, should be considered routinely for palliative care patients requiring systemic NSAIDs including COX-2 inhibitors such as celecoxib.

## CHLORPROMAZINE

Largactil®

**Class:** Phenothiazine – antipsychotic, neuroleptic, antiemetic.

**Licensed indications:** Acute and chronic psychoses, short term management of anxiety; agitation or disturbed behaviour in non-psychotic disorders; severe behavioural disorders in children; if non-drug treatment fails.

**Recognised other use(s) in palliative care:** nausea and vomiting, intractable hiccough.

**Contraindications/cautions:** proven allergy to chlorpromazine - consider possibility of cross-sensitivity with other phenothiazines, Parkinson's Disease.

**Specific considerations:**

*Hepatic impairment:* phenothiazines are potentially hepatotoxic and may precipitate coma, avoid in moderate to severe hepatic impairment.

*Renal impairment:* start with small dose in severe renal impairment.

**Adverse reactions:**

*Common:* sedation, anxiety, agitation, extra-pyramidal effects, orthostatic hypotension, tachycardia, photosensitivity, blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention, sexual adverse effects, weight gain, hyperprolactinaemia.

*Less common:* prolongation of the QT interval, SIADH, blood dyscrasias.

**Interactions:**

Chlorpromazine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other anticholinergic drugs.

Additive effects with other CNS depressant drugs.

Additive effects with other drugs that lower seizure threshold.

Additive effects with other drugs that prolong the QT interval, increasing the risk of arrhythmias.

**Dosage:**

Nausea/vomiting:

*IM:* 10-25mg initially, repeated every 3-4 hours until vomiting stops then give orally, reduce dose by half in the elderly.

Agitation, anxiety, disturbed behaviour:

*Oral:* 25–50 mg up to 3 times daily.

Acute psychoses, severe behaviour disturbance:

*Oral:* 50–100 mg up to every 2 hours as needed, up to maximum of 500 mg per day.

Chronic psychoses:

*Oral:* 25–100 mg 3–4 times daily, up to maximum of 1000 mg per day.

**Syringe driver:** not for SC administration as highly irritant, may cause necrosis.

**Mechanism of action:** as an antiemetic has inhibitory effects on the chemoreceptor trigger zone. Antipsychotic effects are manifested through blockade of dopamine (D<sub>2</sub>) receptors, also has anticholinergic, antihistaminic, antiserotonergic and alpha-adrenergic blocking effects.

**Onset:** of action usually within 2 hours of oral dosing.

**Peak:** of action not reported, however plasma levels peak 1 to 4 hours after oral dosing and 15 to 30 minutes after IM injection.

**Duration:** of action may last up to 24 hours after a single dose and the half-life is reported to range from 20 to 40 hours.

**Availability:**

*Tablets:*

10mg, PBS general benefit [100](5)

25mg, PBS general benefit [100](5)

100mg, PBS general benefit [100](5)

*Oral liquid:*

5mg/mL, 100mL, PBS general benefit [1](5)

*Injection:*

25mg/mL 2mL, PBS general benefit [10](0)

Chlorpromazine is only available as the brand Largactil®.

**Notes:**

- do not inject SC, as the solution is highly irritant and may cause necrosis.
- avoid IM injection where possible as this is often very painful.
- in situations where there is no alternative to IM administration, inject deeply into a large muscle mass.
- when injecting IV, dilute with sodium chloride 0.9% to a concentration of not greater than 1mg/mL and administer at a rate of 1mg/minute.

# CHOLESTYRAMINE

Questran Lite®

**Class:** Bile acid binding resin.

**Licensed indications:** itch associated with partial biliary tract obstruction, diarrhoea following ileal resection or disease, hypercholesterolaemia or mixed hyperlipidaemia.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to cholestyramine, impairs absorption of fat-soluble vitamins (A, D, E and K), supplements may be needed for patients taking high doses for long periods.

**Specific considerations:**

*Hepatic impairment:* not absorbed from GI tract, therefore unlikely to be relevant.

*Renal impairment:* not absorbed from GI tract, therefore unlikely to be relevant.

**Adverse reactions:**

*Common:* constipation, flatulence, abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, anorexia.

*Less common:* increased triglycerides.

*Rare:* faecal impaction, aggravation of haemorrhoids, steatorrhoea, decreased absorption of fat-soluble vitamins, increased bleeding tendency, hyperchloraemic acidosis.

**Interactions:**

Cholestyramine can affect drug absorption (both the rate and extent) through a binding effect in the gut and may reduce the effect of: amitriptyline, diclofenac, loperamide, valproate and warfarin.

**Dosage:**

Pruritus:

*Oral:* 4-8g per day is usually sufficient.

Other indications:

*Oral:* initially 4g twice a day, increasing over 2 to 4 weeks to a maintenance dose of 12-16g (maximum 36g) per day in 2 to 3 divided doses.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** binds bile acids in intestine, preventing reabsorption, and increasing bile acid excretion in the faeces, this increases demand for cholesterol for synthesis of bile acids resulting in an increase in uptake and removal of LDL from plasma. In pruritus the reduction of serum bile acid levels reduces excess bile acids deposited in the dermal tissue.

**Onset:** of action variable in pruritus, typically 2 to 3 days.

**Peak:** of action not reported, plasma levels not applicable as not absorbed

**Duration:** of action not reported, plasma levels not applicable as not absorbed

**Availability:**

*Oral liquid (powder sachets):*

4g, PBS general benefit [100](5)

8g, PBS general benefit, [50](5)

Currently only available as the brand Questran Lite®.

**Notes:** none

# CIMETIDINE

Magicul®, Tagamet®

**Ranitidine is generally preferred when a Histamine-2 receptor antagonist is indicated due to the potential for significant drug interactions with cimetidine; cimetidine may however have a role in severe pruritus.**

**Class:** Histamine-2 receptor antagonist (H2RA).

**Licensed indications:** peptic ulcer disease, gastro-oesophageal reflux disease, dyspepsia, scleroderma oesophagus.

**Recognised other use(s) in palliative care:** severe pruritus.

**Contraindications/cautions:** proven allergy to cimetidine.

**Specific considerations:**

*Hepatic impairment:* doses may need to be reduced in hepatic impairment.

*Renal impairment:* doses should be reduced in renal impairment.

**Adverse reactions:**

*Common:* diarrhoea, dizziness, rash and tiredness.

*Less common:* gynaecomastia, decreased libido, impotence, hypotension, confusion.

**Interactions:**

Cimetidine is a potent inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a high risk of clinically significant interactions:

Cimetidine may inhibit the metabolism and increase the concentration and effect of: alprazolam, amitriptyline, carbamazepine, clonazepam, diazepam, fentanyl, flecainide, haloperidol, methadone, midazolam, nortriptyline, phenytoin, warfarin.

Absorption of cimetidine may be decreased by octreotide.

Cimetidine may compete for renal tubular secretion with other drugs excreted by this route.

Cimetidine may decrease the absorption of ketoconazole.

**Dosage:**

*Oral:* GORD 400mg twice daily; PUD 800mg daily as a single evening dose (or as 2 divided doses) for 4–8 weeks, reduced to 400mg daily as a single evening dose (or as 2 divided doses); Dyspepsia 200 mg up to 4 times daily for 4–8 weeks; Severe pruritus: 400mg twice daily.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** inhibits gastric acid secretion via blockade of histamine-2 receptors on parietal cells. In severe pruritus, blockade of histamine-2 receptors may provide additional efficacy over that from blockade of histamine-1 receptors alone.

**Onset:** of action within 1 hour.

**Peak:** of action not reported, however plasma levels peak within 1 to 3 hours (at lower end of this range when given on an empty stomach).

**Duration:** of action around 7 hours, half-life is around 2 to 3 hours.

**Availability:**

*Tablets:*

200mg, PBS general benefit [120](5)

400mg, PBS general benefit [60](5)

800mg, PBS general benefit [30](5)

Cimetidine preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- Proton Pump Inhibitors (e.g. omeprazole, esomeprazole or pantoprazole) are the considered the drugs of choice for prophylaxis or treatment of NSAID-induced GI damage, rather than histamine-2 receptor antagonists.

## CITALOPRAM

*Celapram®*, *Celica®*, *Ciazil®*, *Cipramil®*, *Citalobell®*, *Talam®*, *Talohexal®*

**Class:** Antidepressant - SSRI (Selective Serotonin Re-uptake Inhibitor).

**Licensed indications:** depression.

**Recognised other use(s) in palliative care:** anxiety (chronic), neuropathic pain.

**Contraindications/cautions:** proven allergy to citalopram, epilepsy, bleeding disorders, abrupt withdrawal.

**Specific considerations:**

*Hepatic impairment:* dose should be restricted to the lower end of the dose range.

*Renal impairment:* dose adjustment not required in mild to moderate impairment; no information available in severe impairment (creatinine clearance <20 mL / min).

**Adverse reactions:**

*Common:* nausea, sweating, tremor, diarrhoea, constipation, somnolence.

*Less common:* dry mouth, cough, postural hypotension, tachycardia, amnesia, taste disturbance, visual disturbances, pruritus, hyponatraemia, sexual dysfunction.

**Interactions:**

Citalopram is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other serotonergic drugs, increasing risk of serotonin syndrome.

Increased risk of GI bleeding with warfarin and NSAIDs.

**Dosage:**

*Oral:* 10-40mg once per day.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:**

Selectively inhibits the reuptake of serotonin (5-hydroxytryptamine, 5HT).

**Onset:** of action in depression 1 to 2 weeks, in anxiety or pain 3 to 7 days.

**Peak:** of action in depression typically 5 to 6 weeks, plasma levels peak within about 4 hours.

**Duration:** of action not reported, however half-life of citalopram is around 1.5 days.

**Availability:**

*Tablets:*

10mg, PBS restricted benefit [28](5)<sup>1</sup>

20mg, PBS restricted benefit [28](5)<sup>1</sup>

40mg, PBS restricted benefit [28](5)<sup>1</sup>

PBS notes

1. restricted benefit for major depressive disorders

**Notes:**

citalopram has a lower interaction potential than other SSRIs such as fluoxetine.

# CLONAZEPAM

Paxam®, Rivotril®

**Class:** Benzodiazepine – anticonvulsant.

**Licensed indications:** epilepsy refractory to other antiepileptic drugs, in particular absence and myoclonic seizures and infantile spasms; acute treatment of seizures including status epilepticus.

**Recognised other use(s) in palliative care:** sedation, anxiety, agitation, restless leg syndrome, neuropathic pain, dyspnoea, hiccoughs, myoclonic jerks; administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to clonazepam, avoid sudden withdrawal, respiratory depression, adsorbs onto PVC reducing drug availability.

**Specific considerations:**

*Hepatic impairment:* reduce dose in mild to moderate hepatic impairment, avoid in severe hepatic impairment.

*Renal impairment:* dose may need to be reduced in renal impairment.

**Adverse reactions:**

*Common:* fatigue, drowsiness (at higher doses).

*Less common:* respiratory depression, incontinence, co-ordination problems, disinhibition, increase in salivation, confusion.

**Interactions:**

Clonazepam is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of clonazepam may be increased by some cytochrome inhibitors: e.g. cimetidine.

Concentration and effect of clonazepam may be decreased by some cytochrome inducers: e.g. carbamazepine, phenobarbitone, phenytoin, rifampicin.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

**Dosage:**

*Oral:* 0.5-8mg per day, usually in two divided doses (1-2mg per day usually adequate).

*SC:* 1-8mg per day.

**Syringe driver:** see syringe driver compatibility table, note adsorbs onto PVC.

**Mechanism of action:** may enhance the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

**Onset:** of action *Oral:* 20 to 60min; *SC:* 5 to 10min.

**Peak:** of action not reported, however plasma levels peak within 1 to 4 hours.

**Duration:** of action around 12 hours; mean plasma half-life reported to be 30 hours, ranging significantly from 20 to 60 hours.

**Availability:**

*Tablets (scored):*

0.5mg, PBS authority benefit [200](2)<sup>1</sup>, [100](3)<sup>2</sup>, [100](0)<sup>3</sup>

2mg, PBS authority benefit [200](2)<sup>1</sup>, [100](3)<sup>2</sup>, [100](0)<sup>3</sup>

*Oral drops:*

2.5mg/mL (0.1mg/drop), 10ml, PBS authority benefit [2](0)<sup>1</sup>, [2](3)<sup>2</sup>, [2](0)<sup>3</sup>

*Injection (with diluent):*

1mg/mL 1 mL PBS restricted benefit [5](0)<sup>4</sup>

Clonazepam preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. PBS authority required neurologically proven epilepsy.
2. PBS authority required initial supply (for up to 4 months) for palliative care patients for the prevention of epilepsy; continuing supply for palliative care patients for the prevention of epilepsy, where consultation with a palliative care specialist or service has occurred (3 repeats).
3. PBS authority required continuing supply for palliative care patients for the prevention of epilepsy (no repeats).
4. PBS restricted benefit for epilepsy.

**Notes:**

- clonazepam is a long acting benzodiazepine, so difficult to titrate to response.
- benzodiazepines may reduce dyspnoea by their anxiolytic and sedative effects.
- clonazepam is adsorbed onto PVC, therefore glass equipment should be used whenever possible.
- where PVC cannot be avoided, IV infusions (prepared as per manufacturer's advice) should be administered immediately after preparation and at a rate of at 60mL/hour.
- see below for comparison with other benzodiazepines and zopiclone.

<b>Pharmacological properties and dose equivalents* for benzodiazepines and zopiclone</b>					
Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

# CLONIDINE

Catapres®

**Class:** Alpha-2 adrenoreceptor agonist (centrally acting).

**Licensed indications:** hypertension, treatment of menopausal flushing.

**Recognised other use(s) in palliative care:** neuropathic pain, spasticity, diarrhoea or gastroparesis related to autonomic dysfunction in diabetes mellitus, sweating.

**Contraindications/cautions:** proven allergy to clonidine, severe bradycardia due to sick sinus syndrome or heart block, coronary heart disease, heart failure, cerebrovascular disease, Raynaud's syndrome or other vasospastic peripheral vascular disease, depression, diabetes, stopping clonidine abruptly may precipitate a severe withdrawal syndrome.

**Specific considerations:**

*Hepatic impairment:* no specific recommendations in hepatic impairment.

*Renal impairment:* dosage must be adjusted to the individual response, which can show high variability in patients with renal insufficiency; careful monitoring is required.

**Adverse reactions:**

*Common:* drowsiness, dry mouth, headache, constipation, fatigue, weakness, bradycardia.

*Less common:* orthostatic hypotension, dizziness, fluid retention, sleep disturbance, impotence, depression, nausea, vomiting, itching and rash.

**Interactions:**

Additive effects with other drugs that cause bradycardia.

Additive effects with other CNS depressant drugs.

Additive effects with other drugs that cause hypotension.

Tricyclic antidepressants may reduce the hypotensive effect of clonidine leading to increased blood pressure.

**Dosage:**

Initiate at low dose and titrate according to response and adverse effects (e.g. hypotension). If appropriate to stop clonidine treatment, this should be done by gradually reducing the dose over at least 7 days.

*Oral/SC:* Initially 0.05mg at night, increasing at 48 hour intervals to 0.05mg bd and then 0.05mg tds. If effective and tolerated, continue to increase by 0.05mg increments at 48 hour intervals until a dose of 0.15mg tds is reached.

**Syringe driver:** not usually given by syringe driver.

**Mechanism of action:** lowers blood pressure by reducing sympathetic tone mediated via central alpha-2 adrenoreceptor agonist activity; in pain management, appears to have synergistic activity with opioid analgesics.

**Onset:** of action *Oral:* 30–60min, *SC:* not reported.

**Peak:** of action not reported; however plasma levels peak 3 to 5 hours after oral administration, not reported for SC administration

**Duration:** of action between 8 and 24 hours; half life usually 6 to 24 hours but may be up to 40 hours in renal impairment.

**Availability:**

*Tablets (scored):*

0.1mg, PBS general benefit [100](5)

0.15mg, PBS general benefit [100](5)

*Injection:*

0.15mg/mL, 1 mL, Not PBS funded

Currently only available as the Catapres® brand.

**Notes:**

- Clonidine should be withdrawn over at least 7 days, stopping abruptly may precipitate severe withdrawal syndrome.

## CODEINE PHOSPHATE

**Class:** Opioid – analgesic, anti-diarrhoeal and anti-tussive.

**Licensed indications:** mild to moderate pain, cough suppression and diarrhoea.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to codeine or morphine.

**Specific considerations:**

*Hepatic impairment:* dose adjustment may be required, reduce dose and in severe hepatic disease titrate carefully as may precipitate coma.

*Renal impairment:* increased dosing interval may be required as active metabolites accumulate in severe renal impairment.

**Adverse reactions:**

*Common:* nausea, vomiting, constipation, dyspepsia, drowsiness, dizziness, headache, orthostatic hypotension, dry mouth, urinary retention.

*Less common:* dose-related respiratory depression, bronchospasm, confusion, hallucinations, delirium, agitation, mood changes, tremor, visual disturbances, urticaria, hypothermia, bradycardia or tachycardia, hypertension, ureteric or biliary spasm, muscle rigidity, myoclonus (with high doses in palliative care), flushing due to histamine release.

**Interactions:**

Rifampicin may increase metabolism of codeine (and of morphine, the active metabolite), therefore may decrease analgesic effect.

Naloxone is an opioid antagonist which may block the effects of codeine.

Buprenorphine is a partial opioid agonist which may block the effects of codeine.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

**Dosage:**

*Oral:* 30–60mg every 4 hours; maximum 240mg/24 hours.

*SC:* 30–60mg every 4 hours; maximum 240mg/24 hours.

*IM:* 30–60mg every 4 hours; maximum 240mg/24 hours.

**Syringe driver:** not usually given by syringe driver.

**Mechanism of action:** therapeutic effects of codeine result from its metabolism to morphine, which mimics endogenous opioids by activating opioid receptors in the central and peripheral nervous systems.

**Onset:** of action 30 to 60 minutes for analgesia, 1 to 2 hours for antitussive effect.

**Peak:** of action not reported; however plasma concentrations peak within 2 hours.

**Duration:** of action between 4 and 6 hours.

**Availability:**

*Tablets:*

30mg, PBS general benefit [20](0)

*Oral liquid:*

5mg/mL, Not PBS funded

*Injection:*

50mg/mL, 1 mL, Not PBS funded

Codeine preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- 6–10% of Caucasians and 1–2% of Asians lack the enzyme necessary for the metabolism of codeine to morphine, such patients are unlikely to obtain a therapeutic effect with codeine.

## CYCLIZINE

Marzine®, Valoid®

**Class:** Antiemetic – antihistamine.

**Licensed indications:** nausea and vomiting (including motion sickness).

**Recognised other use(s) in palliative care:** administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to cyclizine, prostatic hypertrophy, narrow angle glaucoma.

**Specific considerations:**

*Hepatic impairment:* caution in hepatic disease.

*Renal impairment:* dose reduction may be necessary in patients with renal impairment.

**Adverse reactions:**

*Common:* drowsiness, restlessness, dry mouth, blurred vision, constipation.

*Less common:* insomnia, hallucinations (more common in the elderly), arrhythmias.

**Interactions:**

Additive effects with other anticholinergic drugs.

Additive effects with other CNS depressant drugs.

**Dosage:**

*Oral:* 25–50mg three times a day.

*SC:* 75–150mg/24 hours.

**Syringe driver:** see syringe driver compatibility table.

**Mechanism of action:** acts on the histamine receptors in the vomiting centre in the CNS and has anticholinergic properties.

**Onset:** of action 30 to 60 minutes.

**Peak:** of action 1 to 2 hours.

**Duration:** of action 4 to 6 hours; half life reported to be around 20 hours.

**Availability:**

*Tablets (scored, as hydrochloride):*

50mg, Not PBS funded, available through the Special Access Scheme (SAS).

*Injection (as lactate):*

50mg/mL, Not PBS funded, available through the Special Access Scheme (SAS).

**Notes:**

- Although there is a theoretical interaction with prokinetic antiemetics (prokinetics stimulate the gut while cyclizine slows it down), they are commonly used together and this may be justified on the basis of differential effect on central receptors.

## DEXAMETHASONE

Dexamethasone®

**Class:** Corticosteroid – glucocorticoid.

**Licensed indications:** cerebral oedema (raised intracranial pressure), allergy, anaphylaxis, postoperative or chemotherapy induced nausea and vomiting.

**Recognised other use(s) in palliative care:** nausea and vomiting of other causes, inflammation in gastrointestinal obstruction, sweating, itch, hypercalcaemia, hiccough, pain, dyspnoea (lymphangitis), liver capsule pain, tenesmus, administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to dexamethasone, infections, gastro-intestinal bleeding.

**Specific considerations:**

*Hepatic impairment:* caution and patient monitoring is recommended.

*Renal impairment:* caution and patient monitoring is recommended.

**Adverse reactions:**

*Common:* insomnia (less if given as a single daily dose in the morning).

*Less common:* sodium and fluid retention, gastro-intestinal ulceration, delayed wound healing, thinning of skin (on prolonged use), muscle weakness (proximal myopathy), Cushing's syndrome, weight gain, mania, depression, delirium, hyperglycaemia, osteoporosis.

**Interactions:**

Dexamethasone is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of dexamethasone may be increased by some cytochrome inhibitors: e.g. ketoconazole.

Concentration and effect of dexamethasone may be decreased by some cytochrome inducers: e.g. carbamazepine, phenobarbitone, phenytoin, rifampicin.

Dexamethasone is also an inducer of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Dexamethasone may induce the metabolism and decrease the concentration and effect of: amitriptyline, methadone, midazolam, phenytoin, warfarin.

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

**Dosage:**

*Oral:* 4-32mg/24 hours.

*SC:* 4-16mg/24 hours.

**Syringe driver:** not recommended due to compatibility problems, use by this method is rarely essential as the long duration of action means a once daily SC bolus may be effective. However, priming SC sites with dexamethasone can usefully prolong them. This can be done by injecting a small volume of dexamethasone (e.g. 0.5-1 mg) directly into the infusion site via the cannula that is to be used, flushing with Sodium Chloride 0.9%, then connecting the syringe driver and commencing the infusion.

**Mechanism of action:** decreases inflammatory response, thought to be via induction of the anti-inflammatory protein lipocortin.

**Onset:** of action is variable, typically between 8 and 24 hours.

**Peak:** of action not reported, however plasma levels peak within 1 to 2 hours.

**Duration:** of action between 36 and 54 hours; half-life is 4 to 5 hours.

**Availability:**

*Tablets (scored):*

0.5mg, PBS general benefit [30](4)

4mg, PBS general benefit [30](4)

*Injection:*

4mg/mL, 1mL, PBS general benefit [5](0)

4mg/mL, 2mL, PBS general benefit [5](1)

Dexamethasone preparations may be available from a range of manufacturers and may contain a variety of excipients; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- 0.75mg dexamethasone has an equivalent anti-inflammatory effect to 5mg prednisone or 20mg hydrocortisone.
- when discontinuing dexamethasone decrease the dose slowly (taper), unless the patient has been taking it for less than five days in which case dose tapering is not necessary.
- mood changes not usually seen with doses below 6mg dexamethasone daily.
- corticosteroid-induced mood change is usually depression and rarely mania, paranoia and psychosis can occur.
- corticosteroid-induced insomnia may respond to hypnotics

## **DIAZEPAM**

*Antenex®*, *Ducene®*, *Valium®*, *Valpam®*

**Licensed indications:** acute treatment of seizures, including status epilepticus; muscle spasms.

**Recognised other use(s) in palliative care:** sedation, anxiety, agitation, restless leg syndrome, dyspnoea, hiccoughs, myoclonic jerks.

**Contraindications/cautions:** proven allergy to diazepam, avoid sudden withdrawal, respiratory depression.

### **Specific considerations:**

*Hepatic impairment:* contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present. In mild-to-moderate hepatic impairment, use low doses of a short acting benzodiazepine to reduce risk of precipitating coma.

*Renal impairment:* increased sensitivity to CNS effects in renal impairment, use a lower initial dose in severe impairment.

### **Adverse reactions:**

*Common:* fatigue, drowsiness (at higher doses).

*Less common:* respiratory depression, incontinence, co-ordination problems, disinhibition, increase in salivation, confusion.

### **Interactions:**

Diazepam is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of diazepam may be increased by some cytochrome inhibitors: e.g. cimetidine, esomeprazole, fluconazole, fluoxetine, ketoconazole, omeprazole, valproate.

Concentration and effect of diazepam may be decreased by some cytochrome inducers: e.g. phenytoin and rifampicin.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

### **Dosage:**

Sedation, anxiety, agitation, restless leg syndrome, muscle spasm:

*Oral:* 2–15mg/24 hours in divided doses.

Seizures:

*IV:* 10-20mg, repeated as necessary to a maximum of 50mg over 60 minutes.

*Rectal:* diazepam is often given rectally instead of IV when IV access cannot be obtained; rectal solutions are sometimes made (or obtained) by hospital pharmacy departments but oral or injectable solutions may also be used.

**Syringe driver:** should not be given SC, therefore not applicable.

**Mechanism of action:** may enhance the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

**Onset:** of action *Oral:* within 15 minutes, *IV:* within 5 minutes.

**Peak:** of action not reported; however peak plasma concentrations *Oral:* 30 to 90 minutes, *Rectal:* 10 to 30 minutes.

**Duration:** of action variable, typically in range of 3 to 30 hours; half-life is around 1 or 2 days, however active metabolite (nordiazepam) has a half-life of up to 5 days.

**Availability:***Tablets (scored):*2mg, PBS general benefit [50](0), Palliative Care authority [50](0)<sup>1</sup>, [50](3)<sup>2</sup>

5mg, PBS general benefit [50](0)

*Injection:*5mg/mL, 2mL, PBS general benefit [5](0), Palliative Care authority [50](0)<sup>1</sup>, [50](3)<sup>2</sup>

Diazepam preparations may contain a variety of excipients (e.g. colours), seek further advice in patients with intolerance or hypersensitivity to excipients

PBS notes:

1. initial supply (up to 4 months) for palliative care patients where anxiety is a problem.
2. continuing supply for palliative care patients where anxiety is a problem, and where consultation with a palliative care specialist or service has occurred.

**Notes:** See below for comparison with other benzodiazepines and zopiclone.

<b>Pharmacological properties and dose equivalents* for benzodiazepines and zopiclone</b>					
Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## DICLOFENAC

Diclohexal®, DINAC®, Voltaren®, Fenac®, Dinac®

**Class:** Non-steroidal anti-inflammatory drug (NSAID).

**Licensed indications:** pain associated with inflammation.

**Recognised other use(s) in palliative care:** itch, sweating; administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to diclofenac, gastro-intestinal ulceration, asthma (in NSAID sensitive patients), cardiac impairment.

**Specific considerations:**

*Hepatic impairment:* use with caution in severe impairment; increased risk of bleeding.

*Renal impairment:* pre-existing renal impairment increases the risk of NSAID-induced renal impairment; increased risk of bleeding. Avoid use in moderate-to-severe renal impairment.

**Adverse reactions:**

*Common:* indigestion, gastro-intestinal ulceration (more common in the elderly), diarrhoea, nausea.

*Less common:* dizziness, rash, nephrotoxicity, hepatitis, oedema, hypertension, headache, tinnitus, proctitis (rectal administration), prolonged bleeding time.

**Interactions:**

Diclofenac is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Absorption of diclofenac may be reduced by cholestyramine.

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

Additive effects with other nephrotoxic drugs.

Diclofenac may reduce effect of diuretics and antihypertensives.

**Dosage:**

*Oral / Rectal:* 50-150mg per day in three divided doses.

**Syringe driver:** not usually given by syringe driver.

**Mechanism of action:** inhibits prostaglandin synthesis through the inhibition of cyclo-oxygenase which is present in both COX-1 and COX-2 forms. Inhibition of COX-1 is associated with impaired gastric cytoprotection and anti-platelet function. Inhibition of COX-2 is associated with anti-inflammatory and analgesic action. Reduction in Glomerular Filtration Rate and renal blood flow is associated with both COX-1 and COX-2 inhibition.

**Onset:** of action 20-30 minutes.

**Peak:** of action not reported; however peak plasma levels *IM:* 20 minutes, *Oral:* around 2 hours, *PR:* 1 hour.

**Duration:** of action up to 8 hours.

**Availability:**

*Tablets (enteric coated):*

25mg, PBS restricted benefit [100](3)<sup>1</sup>, Palliative Care authority [100](3)<sup>2</sup>, [100](0)<sup>3</sup>

50mg, PBS restricted benefit [100](3)<sup>1</sup>, Palliative Care authority [100](3)<sup>2</sup>, [100](0)<sup>3</sup>

*Suppositories:*

12.5mg, 25mg & 50mg, Not PBS funded

100mg, PBS restricted benefit [40]<sup>1</sup>, Palliative Care authority [40](3)<sup>2</sup>, [40](0)<sup>3</sup>

Gel:

1%, 20, 50 & 100g, Not PBS funded

Diclofenac preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. chronic arthropathies (including osteoarthritis) with an inflammatory component; bone pain due to malignant disease (3 repeats).
2. initial supply (for up to 4 months) for palliative care patients where severe pain is a problem and continuing supply for these patients where consultation with a palliative care specialist or service has occurred (3 repeats).
3. continuing supply for palliative care patients where severe pain is a problem (no repeats).

**Notes:**

- unless contra-indicated, NSAIDs such as diclofenac should be given alongside regular full-dose paracetamol to provide optimal effect.
- NSAIDs (with paracetamol as above) are an effective co-analgesic when given with opioids in the treatment of bone and soft tissue pain.
- diclofenac is the NSAID of choice in palliative care.
- gastric cytoprotection with a proton pump inhibitor e.g. omeprazole, should be considered routinely for palliative care patients requiring systemic NSAIDs.

## **DOCUSATE**

*Coloxyl*® and in combination: *Coloxyl with Senna*®

**Class:** Laxative – faecal softener and stimulant.

**Licensed indications:** constipation.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to docusate, acute abdominal pain.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

No adverse reactions reported commonly.

*Less common:* abdominal cramps, atonic colon (on prolonged use), bitter taste.

**Interactions:**

May potentially antagonise the effects of antispasmodics e.g. hyoscine butylbromide.

**Dosage:**

Docusate single agent preparation:

*Oral:* 100–150 mg once or twice daily; up to 480 mg per day in divided doses may be used if required.

Docusate with senna preparation:

*Oral:* 1-2 tablets at night, maximum 4 tablets at night.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** as an anionic wetting agent, acts as a faecal softener by lowering the surface tension and allowing penetration of water and salts into faeces, this produces softer stools which facilitate their movement. Also possesses modest stimulant properties.

**Onset:** of action variable, typically 12 to 72 hours

**Peak:** not applicable.

**Duration:** not applicable.

**Availability:**

*Tablets:*

50mg, RPBS benefit only

50mg (with 8mg senna), RPBS benefit only

**Notes:**

- as docusate has some stimulant action it should be avoided in complete intestinal obstruction, in common with other stimulant laxatives.
- as a single agent docusate is not the laxative of choice in opioid induced constipation, but useful in combination with a more potent stimulant.

## **DOMPERIDONE**

Motilium®

**Class:** Antiemetic – prokinetic, dopamine antagonist.

**Licensed indications:** nausea, vomiting, flatulence, gastro-oesophageal reflux.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to domperidone, complete intestinal obstruction, prolonged QT interval, use with ketoconazole or erythromycin contraindicated.

### **Specific considerations:**

*Hepatic impairment:* should not be used in patients with hepatic impairment.

*Renal impairment:* reduce dose if using repeatedly in severe renal impairment.

### **Adverse reactions:**

*Common:* hyperprolactinaemia, breast tenderness.

*Less common:* abdominal cramps, diarrhoea, dry mouth, headache and dizziness.

### **Interactions:**

Domperidone is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that affect this system. The greatest risk is with inhibitors, as these may increase the risk of QT interval prolongation e.g. ketoconazole (do not give with domperidone).

Anticholinergic drugs may reduce prokinetic effects of domperidone.

Additive effects with other drugs that prolong the QT interval, increasing the risk of arrhythmias.

Domperidone may increase absorption of paracetamol.

### **Dosage:**

*Oral:* 10-20mg three to four times a day.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** blocks dopamine receptors in the upper GI tract, chemo-receptor trigger zone (CTZ) and CNS. Similar to metoclopramide although has fewer CNS effects, therefore less likely to cause extra pyramidal side-effects.

**Onset:** of action within 30 minutes.

**Peak:** of action not reported; however plasma levels peak within 30 to 60 minutes.

**Duration:** of action typically around 12 to 24 hours.

### **Availability:**

*Tablets:* 10mg, PBS general benefit [25](0)

Currently only available as the Motilium® brand.

### **Notes:**

- main advantage over metoclopramide is lack of extra pyramidal side effects.
- disadvantage is that it is not available for parenteral administration.
- useful in nausea and vomiting associated with gastric stasis.

## ENOXAPARIN

Clexane® and Clexane Forte®

**Low molecular weight heparins (LMWHs) e.g. enoxaparin, are generally preferred to warfarin when an anticoagulant is indicated in palliative care; as maintaining a stable INR can be problematic due to changes in body weight, dietary intake and clotting pathways associated with disease processes.**

**Class:** Anticoagulant - low-molecular weight heparin (LMWH).

**Licensed indications:** prevention of VTE in surgical patients and in medical patients bedridden due to acute illness, treatment of venous thrombosis, prevention of extracorporeal thrombosis during haemodialysis, treatment of unstable angina and non-ST-segment elevation MI.

**Recognised other use(s) in palliative care:** treatment of pulmonary embolism, pregnancy when full anticoagulation required (seek specialist advice given the rarity of this indication in Palliative Care).

**Contraindications/cautions:** proven allergy to enoxaparin, contraindicated in patients at increased risk of bleeding, including those with thrombocytopenia, bleeding disorders, including haemophilia, peptic ulcer, recent cerebral haemorrhage, severe uncontrolled hypertension, bacterial endocarditis, major trauma or recent surgery (particularly at sites where bleeding would pose a serious risk, e.g. eye or CNS).

Treatment with other drugs which can affect the clotting process may increase the risk of bleeding (but use low dose aspirin where indicated); monitor closely.

Avoid intrathecal or epidural analgesia or anaesthesia, or lumbar puncture; risk of epidural haematoma which may cause paralysis; if procedure considered necessary, seek specialist advice.

Patients with low body-weight (women below 45 kg, men below 57 kg) may be at higher risk of bleeding with prophylactic doses of enoxaparin and require careful monitoring.

### **Specific considerations:**

*Hepatic impairment:* contraindicated in severe hepatic impairment or disease, including oesophageal varices.

*Renal impairment:* doses should be reduced in renal impairment.

### **Adverse reactions:**

*Common:* bruising and pain at injection site, hyperkalaemia, mild reversible thrombocytopenia (does not necessarily indicate increased risk for severe thrombocytopenia).

*Less common:* transient elevation of liver transaminases, haemorrhage, severe thrombocytopenia, skin necrosis (usually at injection site).

### **Interactions:**

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

Additive effects with other drugs that prolong clotting time, increasing risk of bleeding.

Additive effects with other drugs that cause hyperkalaemia.

### **Dosage:**

Prevention of VTE:

SC: Surgical patients, moderate risk, 20mg once daily for 7–10 days or until mobilised, starting 2 hours before surgery. Surgical patients, high risk, 40mg once daily for 7–10 days or

until mobilised, starting 12 hours before surgery. May be continued up to 30 days after total hip replacement surgery. Medical patients, once 40mg daily for 6–14 days or until mobilised.

Treatment of VTE

SC: 1mg/kg twice daily, or 1.5mg/kg once daily, for 5–10 days.

**Syringe driver:** not given by syringe driver.

**Mechanism of action:** Inactivates clotting factors IIa (thrombin) and Xa by binding to antithrombin III; LMWHs have a much greater effect on factor Xa than on thrombin.

**Onset:** of action IV: within 5 minutes; SC: within 3 hours.

**Peak:** of action within 5 hours of SC injection.

**Duration:** of action up to 24 hours after a 40-mg dose; half-life around 4 to 5 hours.

**Availability:**

*Injection:*

20mg/0.2 mL (PFS), PBS general benefit [10](1), restricted benefit [20](3) <sup>1</sup>

40mg/0.4 mL (PFS), PBS general benefit [10](1), restricted benefit [20](3) <sup>1</sup>

60mg/0.6 mL (PFS), PBS general benefit [10](1), restricted benefit [20](3) <sup>1</sup>

80mg/0.8 mL (PFS), PBS general benefit [10](1)

100mg/1 mL (PFS), PBS general benefit [10](1)

120mg/0.8 mL (PFS), PBS general benefit [10](1)

150mg/1 mL (PFS), PBS general benefit [10](1)

Currently only available as the brand Clexane® / Clexane Forte®.

PBS notes:

1. restricted benefit for haemodialysis.

**Notes:**

- Alternate between left and right anterolateral abdominal wall using different site for each injection.
- Injection site should not be rubbed after administration.

## ESOMEPRAZOLE

Nexium®

**Class:** Proton pump inhibitor (PPI) - ulcer healing/prophylactic.

Note: esomeprazole is the S-isomer of omeprazole.

**Licensed indications:** duodenal/gastric ulcer, reflux oesophagitis, dyspepsia, prophylaxis of NSAID induced upper GI toxicity.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to esomeprazole or omeprazole.

### Specific considerations:

*Hepatic impairment:* dose adjustment is not required in mild to moderate hepatic impairment; in severe hepatic impairment dose should not exceed 20mg daily.

*Renal impairment:* dose adjustment is not required in patients with renal impairment, however caution in use is advised in severe renal insufficiency.

### Adverse reactions:

*Common:* headache, nausea, vomiting, diarrhoea, constipation.

*Less common:* insomnia, dizziness, vertigo, pruritus, blood disorders, muscle pain, joint pain, dry mouth, agitation.

### Interactions:

Esomeprazole is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate. (see below for effect esomeprazole may have on other drugs).

Esomeprazole however also inhibits some of the Cytochrome P450 enzymes involved in the metabolism of other drugs and where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Esomeprazole may inhibit the metabolism and increase the concentration and effect of: diazepam, phenytoin and warfarin.

Esomeprazole may decrease the absorption of ketoconazole.

### Dosage:

*Oral:* 10-40mg once a day.

*SC:* injection available but not usually used SC, not stable for any length of time.

**Syringe driver:** not given by syringe driver.

**Mechanism of action:** inhibits gastric acid secretion via proton pump blockade, suppressing both stimulated and basal acid secretion.

**Onset:** of action typically within 30 minutes.

**Peak:** of action not reported, however plasma levels peak after about 1 to 2 hours.

**Duration:** of action up to 24 hours; half-life reported to be around 1.3 hours.

### Availability:

*Tablets (enteric coated):*

20mg, PBS restricted benefit [30](1)<sup>1</sup>, [30](5)<sup>2</sup>

40mg, PBS restricted benefit [30](1)<sup>3</sup>

Currently only available as the brand Nexium®

PBS notes: restricted benefit for

1. restricted benefit for initial treatment of gastric ulcer.
2. restricted benefit for maintenance of healed gastro-oesophageal disease.
3. restricted benefit for healing of gastro-oesophageal disease.

**Notes:**

- Proton Pump Inhibitors are considered the drugs of choice for prophylaxis or treatment of NSAID induced upper GI damage.

## **FENTANYL**

Actiq®, Durogesic®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid.

**Licensed indications:** severe pain, opioid adjunct under anaesthesia, severe chronic pain, breakthrough pain (lozenge).

**Recognised other use(s) in palliative care:** administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to fentanyl. Note: past nausea or hallucinations with opioids are not contraindications.

### **Specific considerations:**

*Hepatic impairment:* dose adjustment may be required in hepatic impairment.

Reduce dose and titrate carefully in severe hepatic disease as may precipitate coma.

*Renal impairment:* current evidence suggests that fentanyl has no active or toxic metabolites and may be used in severe renal impairment when other opioids are inappropriate.

### **Adverse reactions:**

**The Tasmanian Palliative Care Service does not consider it is appropriate to initiate opioid therapy with the "low dose" Fentanyl (0.012mg/hr) patch in patients with cancer pain and advises that opioid naive patients should be titrated with quick release opioids until a steady state is reached and then converted to a patch.**

All opioids share a common range of adverse effects, although these are dose dependent and affected by circumstances of use. There is however significant variation between individuals in their response to different opioids and the different opioids have metabolites which may add to the adverse effects. Switching (rotating) to another, chemically distinct, opioid may therefore be useful to reduce adverse effects by allowing a wash out of these metabolites and presenting the mu receptors with a "fresh" opioid configuration.

*Common:* **Constipation occurs in up to 90% of patients on opioids, always ensure there is a bowel control plan with laxatives.** Although fentanyl is less constipating than morphine, this increases with continued use. Nausea and vomiting are usually transient in the first few (1-5) days and may require metoclopramide or haloperidol to prevent symptoms. Transient confusion and sedation are also common; if persistent they will necessitate a reduction in the opioid dose or switching to another opioid. Dry mouth, dizziness and visual difficulty (particularly problems with accommodation) are also common.

*Less common:* respiratory depression (usually only at high doses but does occur in the opioid naive when there is no titration of dosage, naloxone can reverse respiratory depression but will also reverse analgesia), myoclonic jerking, delirium, pruritus.

Respiratory depression is a serious side effect of opioids but is a symptom which is uncommon in Palliative Medicine where titration of opioids to pain or breathlessness is the norm. Respiratory rate reduction is often a late manifestation of opioid toxicity, but sedation is a better indicator and can be monitored by using a sedation score such as:

<b>Sedation Score</b>	
Score	Sedation level
0	wide awake
1	easy to rouse
2	easy to rouse, but cannot stay awake
3	difficult to rouse
With opioids, the aim is to keep sedation to a level of less than 2 on this scale.	

Adverse effects, including respiratory depression, may persist for longer when fentanyl is given in the form of patches due to the depot effect (it takes at least 17 hours after patch removal for the plasma concentration to drop by 50%) and where there has been accumulation e.g. due to hepatic impairment; extended monitoring may therefore be required.

Rare: visual hallucinations, hyperalgesia, biliary/urinary tract spasm, physical dependence (irrelevant in palliative care), SIADH, anaphylaxis, seizure.

**Interactions:**

Fentanyl is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of fentanyl may be increased by some cytochrome inhibitors: e.g. cimetidine, fluconazole, ketoconazole.

Concentration and effect of fentanyl may be decreased by some cytochrome inducers: e.g. carbamazepine, phenobarbitone, phenytoin.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

**Dosage:**

*Patch:* 0.012–0.3mg/hour (each patch lasts for 3 days).

*Lozenge:* initially 0.2mg, repeated once only in 30 minutes if required. If a single lozenge is inadequate for several episodes of breakthrough pain, use the next dosage strength. The aim is to relieve an episode of breakthrough pain with a single lozenge. If > 4 breakthrough doses required per day, adjust dose of regular baseline opioid.

*SC:* 0.05-0.3mg in 24 hours.

**Syringe driver:**

See syringe driver compatibility chart. Note that data is less extensive than for some other opioids, may therefore require infusion on its own. As fentanyl is only available in a fixed strength / unit volume, this precludes administration of doses >0.6mg by syringe driver. Where higher doses required, sufentanil or hydromorphone may be more appropriate.

**Mechanism of action:** stimulates mu (and other) opioid receptors in the descending inhibitory pathways of the CNS and in the GIT.

**Onset:** of action *Lozenge:* 5-10 minutes; *Patch:* 3 to 24 hours.

**Peak:** of action *Lozenge:* 5-15 minutes; *Intravenous:* 2-3 minutes; *Subcutaneous:* 5-8 minutes; *Patch:* 24 hours after application.

**Duration:** of action *Lozenge:* up to 6 hours; *Patch:* 72 hours (plus depot effect, see notes).

**Availability:**

*Lozenge:*

0.2mg, PBS restricted benefit [3](0)<sup>2</sup>, Palliative Care authority [20](2)<sup>3</sup>, [20](0)<sup>4</sup>

0.4mg, PBS restricted benefit [3](0)<sup>2</sup>, Palliative Care authority [20](2)<sup>3</sup>

0.6mg, PBS restricted benefit [3](0)<sup>2</sup>, Palliative Care authority [20](2)<sup>3</sup>

0.8mg, PBS restricted benefit [3](0)<sup>2</sup>, Palliative Care authority [20](2)<sup>3</sup>

1.2mg, PBS restricted benefit [3](0)<sup>2</sup>, Palliative Care authority [20](2)<sup>3</sup>, [20](0)<sup>4</sup>

1.6mg, PBS restricted benefit [3](0)<sup>2</sup>, Palliative Care authority [20](2)<sup>3</sup>, [20](0)<sup>4</sup>

*Injection:*

0.05mg/mL, 2 mL, 10mL & 20 mL, Not PBS funded

*Transdermal patch:*

0.012mg/hour, PBS restricted benefit [5](0)<sup>1</sup>

0.025mg/hour, PBS restricted benefit [5](0)<sup>1</sup>

0.05mg/hour, PBS restricted benefit [5](0)<sup>1</sup>

0.075mg/hour, PBS restricted benefit [5](0)<sup>1</sup>

0.1mg/hour, PBS restricted benefit [5](0)<sup>1</sup>

Some fentanyl preparations are available from a range of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**PBS notes:**

1. chronic severe disabling pain unresponsive to non-narcotic analgesics.
2. initial supply for dose titration for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects.
3. first continuing supply (for up to 3 months) for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects; OR, second and subsequent continuing supply (for up to 3 months) for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects, where consultation with a palliative care specialist or service has occurred.
4. second and subsequent continuing supply (for up to 1 month) for breakthrough pain in palliative care patients with cancer who are receiving opioids for their persistent pain and where further escalation in the dose of morphine for breakthrough pain results in intolerable adverse effects.

**Notes:**

- paracetamol and an NSAID are effective co-analgesics when given with opioids such as fentanyl in the treatment of bone and soft tissue pain.
- **in Tasmania fentanyl transdermal patches are restricted through state regulation to the management of pain due to malignancy only.**
- **the Tasmanian Palliative Care Service does not consider it is appropriate to initiate opioid therapy with the "low dose" fentanyl (0.012mg/hr) patch in patients with cancer pain.**
- **opioid naive patients should be titrated with quick release opioids until a steady state is reached and then converted to a patch.**
- **fentanyl patches are not suitable for unstable pain situations.**
- converting from transdermal fentanyl to oral morphine
  - equivalence data may not be reliable, due to the differences in absorption and distribution of fentanyl between individuals.
  - the manufacturer's recommendations are a guide but specialist advice may be useful; it is often safer to start low and re-titrate with breakthrough doses, than to precipitate opioid toxicity.

- a useful approach for back titration is to take the breakthrough dose of morphine as the basis for conversion to regular oral morphine.
- e.g. if a patient with a fentanyl 0.1mg/hr patch is comfortable with 15mg of morphine for breakthrough pain, a reasonable maintenance dose of morphine would be 6x15mg, i.e. 90mg/24hrs; whereas other sources including the manufacturer suggest significantly higher doses.
- converting from oral morphine to transdermal fentanyl
  - equivalence data may not be reliable, due to the differences in absorption and distribution of fentanyl between individuals.
  - the Tasmanian Palliative Care Service suggests the conversion ratio for morphine (oral) to fentanyl (SC or transdermal) = 150 : 1
  - i.e. 10mg morphine (oral) = 0.067mg fentanyl (SC or transdermal)
  - the following may provide a useful guide to dose conversions:

<b>Suggested conversion rates for oral morphine to transdermal fentanyl:</b>	
<b>Oral morphine: mg/24 hours</b>	<b>Transdermal fentanyl: micrograms/hour</b>
<60	12
60-100	25
120-200	50
180-300	75
240-400	100
> 400	Seek advice
<b>Please note that <u>micrograms</u> (rather than mg) are used as the units for <u>fentanyl release rates</u> in this table.</b>	

- the absorption of fentanyl from patches will be increased if the patient is febrile.
- the absorption of fentanyl from patches will be increased if the patch comes into contact with direct sources of heat such as electric blankets, heat pads, heat lamps, saunas; avoid such contact where possible.
- write the date and time of application on the patch with a permanent marker (or a ball point pen if a marker is not available).
- patches should not be applied after a hot bath or shower.
- patches should be applied to dry, hairless, non-irritated skin on the upper part of the body or upper arm.
- patch application sites should be rotated to reduce the risk of irritation.
- after removing a patch, avoid exposing that area of skin to the sun for 2 days as it may be more sensitive.
- after removal, used patches should be folded so that the adhesive side of the patch adheres to itself, then wrapped and disposed of safely.
- dose adjustments for patches should usually be done every 3 days.

## **ACUTE TOXICITY**

- **decrease in mental status, respiratory rate and blood pressure. Give naloxone 0.4mg IV repeated as required, up to a maximum of 10mg.**
- **fentanyl patches create a depot in the skin which continues to release fentanyl after removal of the patch. It takes at least 17 hours for concentrations to drop by 50%.**
- morphine or SC fentanyl may be used for breakthrough analgesia in patients using transdermal fentanyl
- if using morphine for breakthrough analgesia, the following may serve as a useful guide to doses:

## Fentanyl Patches – a guide to morphine doses for breakthrough analgesia

Fentanyl patch strength	Fentanyl delivery rate	24 hr oral morphine dose	*Oral morphine breakthrough dose (approx. 1/6 <sup>th</sup> 24 hr dose)	24 hr SC morphine dose	*SC morphine breakthrough dose (approx. 1/6 <sup>th</sup> 24 hr dose)
Fentanyl 12 micrograms /hr (Durogesic® 12) Note: each patch contains total of 2.1mg fentanyl	288 micrograms/24 hr	30 - 50 mg/24 hr	5 – 8 mg	10 - 15 mg/24 hr	1 - 3mg
Fentanyl 25 micrograms /hr (Durogesic® 25) Note: each patch contains total of 4.2 mg fentanyl	600 micrograms/24 hr	60 - 100 mg/24 hr	10 - 15 mg	20 - 35 mg/24 hr	3 - 7.5mg
Fentanyl 50 micrograms /hr (Durogesic® 50) Note: each patch contains total of 8.4 mg fentanyl	1200 micrograms/24 hr	120 - 200 mg/24 hr	20 - 30 mg	40 - 65 mg/24 hr	7.5 - 12.5 mg
Fentanyl 75 micrograms /hr (Durogesic® 75) Note: each patch contains total of 12.6 mg fentanyl	1800 micrograms/24 hr	180 - 300 mg/24 hr	30 - 50 mg	60 - 100 mg/24 hr	10 - 20 mg
Fentanyl 100 micrograms /hr (Durogesic® 100) Note: each patch contains total of 16.8 mg fentanyl	2400 micrograms/24 hr	240 - 400 mg/24 hr	40 - 60 mg	80 - 130 mg/24 hr	15 - 25 mg

\*Due to the variable and unpredictable rate of absorption from fentanyl patches, it is advised to be conservative when prescribing breakthrough analgesia and to titrate to effect.

**Please note that micrograms (rather than mg) are used as the units for fentanyl release rates in this table.**

## **FLECAINIDE**

*Tambacor®*, *Flecatab®*

**Class:** Antiarrhythmic.

**Licensed indications:** supra-ventricular tachycardia, paroxysmal atrial fibrillation or atrial flutter associated with haemodynamic impairment, serious ventricular arrhythmias refractory to other treatment (including DC shock).

**Recognised other use(s) in palliative care:** neuropathic pain.

**Contraindications/cautions:** proven allergy to flecainide, recent myocardial infarction, decreased cardiac output.

**Specific considerations:**

*Hepatic impairment:* reduce dose according to plasma concentration (see notes).

*Renal impairment:* reduce dose according to plasma concentration (see notes).

**Adverse reactions:**

*Common:* nausea, vomiting, constipation, dizziness, blurred vision.

*Less common:* cardiac arrhythmias, hypotension.

*Rare:* cardiac arrest, sudden death, re-entrant arrhythmias in post-MI patients.

**Interactions:**

Flecainide is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of flecainide may be increased by some cytochrome inhibitors: e.g. cimetidine, fluoxetine, haloperidol.

Concentration and effect of flecainide may be decreased by some cytochrome inducers: e.g. carbamazepine, phenobarbitone, phenytoin and tobacco smoke.

Absorption of flecainide may be affected by opioids or prokinetics.

Additive effects with other cardiotoxic drugs.

**Dosage:**

Pain:

*Oral:* Initiate therapy with 50mg twice daily and gradually increase every 3-7 days to maximum of 200mg twice daily.

**Syringe driver:** not given parenterally in pain management, therefore not applicable.

**Mechanism of action:** in pain thought to decrease excitability of nerve cells through stabilisation of the neural membrane. In arrhythmias it increases the refractory period in myocardial tissue.

**Onset:** of action not reported for pain, however 0.5 to 2 hours as anti-arrhythmic.

**Peak:** of action not reported; however plasma levels peak within 2 to 6 hours.

**Duration:** of action not reported for pain; however 15 to 23 hours as anti-arrhythmic.

**Availability:**

*Tablets (scored and unscored):*

50mg, PBS restricted benefit [60](5)<sup>1</sup>

100mg, PBS restricted benefit [60](5)<sup>1</sup>

Flecainide preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

- I. Restricted benefit for treatment of serious cardiac arrhythmias, if ventricular arrhythmia treatment must be initiated in a hospital (inpatient or outpatient).

**Notes:**

- normal therapeutic range for flecainide is 0.2 to 0.9 mg/L.

## FLUCONAZOLE

Diflucan®, Dizole®, Dizole One®, Fluzole®, Ozole®

**Class:** Antifungal – triazole.

**Licensed indications:** fungal infections; acute or recurrent mucocutaneous candidiasis; vulvovaginal candidiasis where topical therapy has failed; candidiasis due to susceptible strains of *Candida* (not *C. krusei* or *C. glabrata*); Tinea corporis, cruris or pedis resistant to topical therapy; onychomycosis (if alternatives have failed or are not tolerated); treatment and prophylaxis of cryptococcal meningitis if amphotericin is not tolerated, or after initial treatment with amphotericin; Coccidioidomycosis; Cryptococcosis; histoplasmosis; prophylaxis/prevention of relapse of candidal infection in immunocompromised people.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to fluconazole - consider possibility of cross-reactivity with other azoles.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* normal initial doses should be given on the first day of treatment and subsequent doses adjusted according to creatinine clearance.

**Adverse reactions:**

*Common:* gastrointestinal upset, headache.

*Less common:* rash (discontinue), blood disorders, arrhythmias, dizziness, convulsions, hypokalaemia.

**Interactions:**

Fluconazole is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate. (see below for effect fluconazole may have on other drugs).

Fluconazole is however also a potent inhibitor of some of the Cytochrome P450 enzymes involved in metabolism of other drugs and where these drugs have a narrow therapeutic range, there is a high risk of clinically significant interactions:

Fluconazole may inhibit the metabolism and increase the concentration and effect of: alprazolam, amitriptyline, carbamazepine, diazepam, fentanyl, methadone, midazolam, oxycodone, phenytoin, warfarin.

**Dosage:**

*Oral:*

vaginal candidiasis: 150mg as a single dose.

oropharyngeal candidiasis: 50-100mg daily for 7 days.

systemic candidiasis: 200–400mg daily (higher doses may be required in neutropenic patients).

prophylaxis in malignancy: 50mg daily.

cryptococcal infections: 200-400mg daily for 7 days.

*IV:* refer to manufacturers information.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** impairs synthesis of ergosterol, increasing permeability of fungal cell membrane and susceptibility to lytic activity by the host defence system.

**Onset:** of action not reported.

**Peak:** of action not reported; however plasma levels peak within 0.5 to 2 hours.

**Duration:** of action not reported; however half-life is around 30 hours.

**Availability:**

*Capsules:*

50mg, PBS authority benefit [28](5) <sup>1</sup>

100mg, PBS authority benefit [28](5) <sup>1</sup>

150mg, Not PBS funded

200mg, PBS authority benefit [28](5) <sup>1</sup>

*Oral liquid:*

10mg/mL (powder), 35mL, Non PBS funded

*Injection:*

2mg/mL, 50mL & 100mL, PBS authority benefit [7](0) <sup>1</sup>

Fluconazole preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

- I. PBS authority required for treatment of cryptococcal meningitis in patients unable to take or tolerate amphotericin; maintenance therapy in patients with cryptococcal meningitis and immunosuppression; treatment of oropharyngeal candidiasis in immunosuppressed patients; treatment of oesophageal candidiasis in immunosuppressed patients; secondary prophylaxis of oropharyngeal candidiasis in immunosuppressed patients; treatment of serious and life-threatening candidal infections in patients unable to tolerate amphotericin.

**Notes:**

- although involved in many interactions, may be less likely to interact with other cytochrome metabolised drugs than ketoconazole (see above).
- useful in severe or recurrent fungal infections.

## **FLUNITRAZEPAM**

*Hypnodorm®*

**Class:** Benzodiazepine – hypnotic.

**Licensed indications:** insomnia.

**Recognised other use(s) in palliative care:** sedation, anxiety, agitation, restless leg syndrome, muscle spasms, dyspnoea, hiccoughs, myoclonic jerks.

**Contraindications/cautions:** proven allergy to flunitrazepam, avoid sudden withdrawal, respiratory depression.

**Specific considerations:**

*Hepatic impairment:* contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present. In mild-to-moderate hepatic impairment, use low doses of a short acting benzodiazepine to reduce risk of precipitating coma.

*Renal impairment:* increased sensitivity to CNS effects in renal impairment; use a lower initial dose in severe impairment.

**Adverse reactions:**

*Common:* fatigue, drowsiness (at higher doses).

*Less common:* respiratory depression, incontinence, co-ordination problems, disinhibition, increase in salivation, confusion.

**Interactions:**

Flunitrazepam is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. Although there are few reports of interactions specifically affecting flunitrazepam, some of the interactions known to affect other benzodiazepines e.g. diazepam or midazolam may also apply to flunitrazepam. However, in the absence of data specific to flunitrazepam, concerns about interactions should not deter efforts to optimise symptom control where appropriate.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

**Dosage:** 0.5-2mg at night.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** may enhance the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

**Onset:** of action within 30 minutes.

**Peak:** of action not reported; however plasma levels peak within 45 minutes.

**Duration:** of action not reported; however half-life of flunitrazepam is around 16 to 35 hours and the half-life of its active metabolites is also reported to be in this range.

**Availability:**

*Tablets:*

1mg (scored), RPBS restricted benefit only

PBS notes: Repatriation PBS restriction to patients with terminal disease; patients with refractory phobic or anxiety states.

**Notes:**

- flunitrazepam was also formerly known by the brand name *Rohypno®* which has been widely abused and needs to be prescribed with caution.
- see below for comparison with other benzodiazepines and zopiclone.

**Pharmacological properties and dose equivalents\* for benzodiazepines and zopiclone**

Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## FLUOXETINE

Prozac®, Lovan®, Fluohexal®, Auscap®, Zactin®, Fluoxebell®

**Class:** Antidepressant - SSRI (Selective Serotonin Re-uptake Inhibitor).

**Licensed indications:** depression, bulimia nervosa, obsessive-compulsive disorder.

**Recognised other use(s) in palliative care:** neuropathic pain, anxiety (chronic).

**Contraindications/cautions:** proven allergy to fluoxetine, epilepsy, bleeding disorders.

**Specific considerations:**

*Hepatic impairment:* halve dose in severe hepatic impairment.

*Renal impairment:* not reported to require dose adjustment in renal impairment.

**Adverse reactions:**

*Common:* nausea, sweating, tremor, diarrhoea, taste disturbance, sexual dysfunction.

*Less common:* dry mouth, cough, constipation, postural hypotension, tachycardia, somnolence, visual disturbances, pruritus, hyponatraemia.

**Interactions:**

Fluoxetine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate. (see below for effect fluoxetine may have on other drugs).

Additive effects with other serotonergic drugs, increasing risk of serotonin syndrome

Increased risk of bleeding with warfarin and NSAIDs.

Fluoxetine is an inhibitor of the Cytochrome P450 system involved in the metabolism of other drug and where these drugs have a narrow therapeutic range there is a risk of clinically significant interactions:

Fluoxetine may inhibit the metabolism and increase the concentration and effect of: alprazolam, amitriptyline, carbamazepine, diazepam, flecainide, haloperidol, methadone, mexiletine, midazolam, nortriptyline, olanzapine, phenytoin, risperidone, and warfarin.

Fluoxetine may lead to increased or decreased levels of valproate.

**Dosage:**

*Oral:* 20-60mg once daily in the morning.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:**

Selectively inhibits the reuptake of serotonin (5-hydroxytryptamine, 5HT), a neurotransmitter in the CNS.

**Onset:** of action in depression and anxiety 1 to 2 weeks, in pain 3 to 7 days.

**Peak:** of action in depression 5 to 6 weeks; plasma levels peak after 6 to 8 hours.

**Duration:** of action not reported; however half-life of fluoxetine is 4 to 6 days and that of the active metabolite norfluoxetine is 4 to 16 days.

**Availability:**

*Tablets:*

20mg, PBS restricted benefit<sup>1</sup>.

*Capsules:*

20mg, PBS restricted benefit<sup>1</sup>.

Fluoxetine preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

I. restricted benefit for major depressive disorder, obsessive-compulsive disorder.

**Notes:**

- note that the main metabolite (norfluoxetine) has a longer half-life than fluoxetine itself.
- watch for serotonin syndrome if switching antidepressants as it takes four to five half-lives to clear most of a drug from the body, which on average may be 44 to 55 days for fluoxetine/norfluoxetine.
- withdrawal symptoms on cessation of fluoxetine are less likely to occur than with other SSRIs, due to the long half-life of fluoxetine/norfluoxetine.
- tablet formulations can be dispersed in water allowing dosing increments of less than 20mg, capsule contents are also dispersible in water.

## **FRUSEMIDE (FUROSEMIDE)**

Frusehexal®, Frusid®, Lasix®, Lasix High Dose®, Lasix M®, Uremide®, Urex®, Urex Forte®, Urex M®

**Class:** Loop diuretic.

**Licensed indications:** oedema associated with heart failure, hepatic cirrhosis, renal impairment and nephrotic syndrome.

**Recognised other use(s) in palliative care:** administration by nebuliser (specialist use only).

**Contraindications/cautions:** proven allergy to frusemide, prostatic obstruction, gout, severe sodium or fluid depletion, treatment with other ototoxic drugs, treatment with potassium-lowering drugs, treatment with nephrotoxic drugs, anuria, elderly patients have greater susceptibility to orthostatic hypotension and electrolytic disturbance.

### **Specific considerations:**

*Hepatic impairment:* diuretic-induced electrolyte imbalance may precipitate hepatic encephalopathy in hepatic impairment.

*Renal impairment:* contraindicated in anuria. Higher doses usually required in renal impairment; renal function may worsen; monitor electrolytes and creatinine.

### **Adverse reactions:**

Most adverse effects are dose-related.

*Common:* hyponatraemia, hypokalaemia, hypomagnesaemia, dizziness, orthostatic hypotension, syncope, dehydration, hyperuricaemia, gout.

*Less common:* increased creatinine concentration, rash, dyslipidaemia, hypocalcaemia.

### **Interactions:**

NSAIDs reduce effects of frusemide.

Phenytoin may reduce effects of frusemide.

Additive effects with other diuretics and drugs causing electrolyte disturbance.

Additive effects with other drugs that cause hypotension.

Additive effects with other nephrotoxic drugs.

Additive effects with other ototoxic drugs.

### **Dosage:**

*Oral:* initially 20–40mg once or twice daily, adjusted according to clinical response to usual maintenance dose range of 20–400mg daily; maximum dose 1g daily.

*IV/IM:* 20–40mg every 1–2 hours until the desired diuretic effect is obtained, increase dose by 20mg each time if necessary.

*Nebuliser:* specialist use only.

**Syringe driver:** not given by syringe driver.

**Mechanism of action:** inhibits the reabsorption of sodium and chloride in the ascending limb of the loop of Henle. As this site accounts for the retention of approximately 20% of filtered sodium, this produces a potent diuresis.

**Onset:** of action *Oral:* 30 to 60 minutes; *IV:* 2 to 5 minutes; *SC:* 30 minutes.

**Peak:** of action around 1 to 2 hours after oral dosing.

**Duration:** of action *Oral:* 4 to 6 hours; *IV:* 2 hours; *SC:* 4 hours.

### **Availability:**

*Tablets (scored and unscored):*

20mg, PBS general benefit [100](1)

40mg, PBS general benefit [100](1)

500mg, PBS general benefit [50](3)

*Oral liquid:*

10mg/mL, 30 mL, PBS general benefit [1](3)

*Injection:*

10mg/mL, 2 mL, PBS general benefit [5](0)

10mg/mL, 4 mL, Not PBS funded

10mg/mL, 25 mL, Not PBS funded

Furosemide preparations are available from a range of manufacturers and may contain a variety of excipients; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- IV doses up to and including 80mg may be given over 2 to 5 minutes.

## GABAPENTIN

*Gabahexal®*, *Gabaran®*, *Gantin®*, *Neurontin®*, *Nupentin®*, *Pendine®*,

**Class:** Antiepileptic – sodium channel blocker.

**Licensed indications:** partial seizures, neuropathic pain in adults.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to gabapentin, risk of aggravation of absence seizures.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* reduce dose in renal impairment.

**Adverse effects:**

*Common:* fatigue, sedation, dizziness, ataxia, tremor, diplopia, nystagmus, amnesia, amblyopia, abnormal thinking, hypertension, vasodilatation, peripheral oedema, dry mouth, weight gain, rash.

*Infrequent:* confusion, psychosis, hypoaesthesia, vertigo.

*Rare:* jaundice, movement disorders, allergic reactions.

**Interactions:**

Additive effects with other CNS depressant drugs.

**Dosage**

Partial seizures:

*Oral:* 300mg on the first day at bedtime, increase by 300mg daily up to 900-1800mg daily in three doses (up to 3600mg daily may be required in some patients).

Neuropathic pain:

*Oral:* initially 100–300mg at night; increase dose gradually every 3–7 days according to response; usual range 1800–3600mg daily in three doses.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** gabapentin is structurally related to gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system, however its precise mechanism of action is not fully understood.

**Onset:** of action variable, typically 24-48 hours.

**Peak:** of action not reported; however plasma levels peak within 2 to 3 hours.

**Duration:** of action around 8 to 12 hours.

**Availability:**

*Capsules:*

100mg, PBS authority benefit [100](5)<sup>1</sup>, RPBS authority benefit, [100](5)<sup>2</sup>

300mg, PBS authority benefit [100](5)<sup>1</sup>, RPBS authority benefit, [100](5)<sup>2</sup>

400mg, PBS authority benefit [100](5)<sup>1</sup>, RPBS authority benefit, [100](5)<sup>2</sup>

*Tablets: (scored and unscored):*

600mg, RPBS authority benefit, [100](5)<sup>2</sup>

800mg, RPBS authority benefit, [100](5)<sup>2</sup>

Gabapentin preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS Notes:

1. PBS authority: treatment of partial epileptic seizures which are not controlled satisfactorily by other anti-epileptic drugs
2. RPBS authority: for the treatment of refractory neuropathic pain not controlled by other drugs

**Notes:** none

## GLYCERINE (GLYCEROL)

**Class:** Laxative – lubricant and osmotic.

**Licensed indications:** constipation.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** none reported.

**Specific considerations:**

*Hepatic impairment:* does not require dose adjustment.

*Renal impairment:* does not require dose adjustment.

**Adverse Reactions:**

*Common:* rectal discomfort.

*Rare:* rectal mucosal erosion.

**Interactions:** none known.

**Dosage:**

*Rectal:* 1 adult suppository once daily when required.

**Syringe driver:** not applicable.

**Mode of action:** Non-absorbable sugar. Osmotic laxative, draws water into faeces, has lubricating properties and may also act as a stimulant by its local irritant effects.

**Onset:** of action within 15 to 30 minutes.

**Peak:** not applicable.

**Duration:** not applicable.

**Availability:**

*Suppository:*

700mg (infants), PBS restricted benefit [3](5)<sup>1</sup>, Palliative Care authority [3](3)<sup>2</sup>, Palliative Care authority [3](0)<sup>3</sup>

1.4g (children), PBS restricted benefit [3](5)<sup>1</sup>, Palliative Care authority [3](3)<sup>2</sup> Palliative Care authority [3](0)<sup>3</sup>

2.8 g (adults), PBS restricted benefit [3](5)<sup>1</sup>, Palliative Care authority [3](3)<sup>2</sup> Palliative Care authority [3](0)<sup>3</sup>, RPBS restricted benefit [3](0)<sup>4</sup>,

PBS Notes:

1. paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function; patients who are receiving long-term nursing care on account of age, infirmity or other condition in hospitals, nursing homes or residential facilities; for use by a patient who is receiving long-term nursing care and in respect of whom a Carer Allowance is payable as a disabled adult; patients receiving palliative care; terminal malignant neoplasia; anorectal congenital abnormalities; megacolon.
2. initial supply (for up to 4 months) for palliative care patients where constipation is a problem; continuing supply for palliative care patients where constipation is a problem, and where consultation with a palliative care specialist or service has occurred.
3. continuing supply for palliative care patients where constipation is a problem.
4. short-term use when oral laxative therapy has failed or is inappropriate.

**Notes:** none.

## GLYCOPYRRONIUM (GLYCOPYRROLATE)

Robinul®

**Class:** Anticholinergic – antisecretory, antispasmodic.

**Licensed indications:** antisecretory premedication, reversal of neuromuscular blockade.

**Recognised other use(s) in palliative care:** excess retained secretions (“death rattle”); administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to glycopyrronium, urinary retention, cardiac disease, glaucoma.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* duration of action may be prolonged in renal impairment, lower doses may be effective.

**Adverse reactions:**

*Common:* dry mouth, tachycardia.

*Less common:* urinary retention, visual problems, dizziness, constipation, drowsiness.

**Interactions:**

Additive effects with other anticholinergic drugs.

Glycopyrronium may antagonise prokinetic effects of metoclopramide and domperidone.

**Dosage:**

*Oral:* 0.2-0.4mg tds.

*SC:* 0.2-0.6mg/24 hours.

**Syringe driver:** see syringe driver compatibility chart.

**Mechanism of action:** blocks muscarinic receptors and reduces secretions.

**Onset:** of action within 30 to 40 minutes.

**Peak effect:** of action not reported.

**Duration:** of action 2 to 3 hours for vagal blocking effects and upto 7 or 8 hours for antisialagogue effects.

**Availability:**

*Injection:*

0.2mg/mL 1 mL & 2 mL, Not PBS funded.

**Notes:**

- Useful alternative when hyoscine hydrobromide has caused confusion.

## HALOPERIDOL

Serenace®, Haldol Decanoate®

**Class:** Antipsychotic / antiemetic – butyrophenone.

**Licensed indications:** nausea and vomiting, mania, schizophrenia.

**Recognised other use(s) in palliative care:** delirium, hiccough; administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to haloperidol, hepatic encephalopathy, epilepsy, Parkinson's disease.

**Specific considerations:**

*Hepatic impairment:* use with caution in hepatic impairment; consider dose reduction.

*Renal impairment:* use with caution in renal impairment.

**Adverse reactions:**

*Common:* extra pyramidal symptoms (usually with doses above 5mg/24 hours) e.g. oculogyric crisis, dystonia, tremor, abnormal movements, restlessness.

*Less common:* hyperprolactinaemia, dry mouth, sedation, arrhythmias.

**Interactions:**

Haloperidol is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of haloperidol may be increased by some cytochrome inhibitors: e.g. cimetidine, fluoxetine and venlafaxine.

Concentration and effect of haloperidol may be decreased by some cytochrome inducers: e.g. carbamazepine, phenytoin, rifampicin and tobacco smoke.

Additive effects with other anticholinergic drugs.

Additive effects with other CNS depressant drugs.

Haloperidol is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Haloperidol may increase the concentration and effect of: amitriptyline, carbamazepine, flecainide, mexiletine, nortriptyline.

**Dosage:**

Nausea/vomiting:

*Oral:* 1.5-3 mg once a day.

*SC:* 1-2mg/24 hours.

Delirium (Note: 1<sup>st</sup> line treatment, both oral and SC routes are reliable options):

Dose and route dependent on severity of symptoms, refer to table below. The primary pharmacological intervention for delirium is to tranquillise (to control psychotic features), occasionally sedation (to induce sleep) is an additional requirement. An anticholinergic agent (e.g. benztropine 2mg) should only be added if extra-pyramidal symptoms appear.

<b>Haloperidol regimen in acute delirium:</b>		
Symptoms	Dose regime	Maximum per 24 hours
Mild - Night time / mild confusion - Day time / hypoactive	*Oral: 0.5mg nocte and 0.5mg PRN *Oral: 0.5mg mane and 0.5mg PRN	2mg 2mg
Moderate / Hyperactive	*Oral: 0.5-1mg TDS and 0.5mg PRN	10mg
Severe #	SC or IV: 5-20mg	20mg
* Administer orally if compliant, SC or IV if not # Replacing haloperidol with a sedating neuroleptic e.g. olanzapine or adding a benzodiazepine (short acting midazolam or longer acting clonazepam) to haloperidol may be options at this stage		

**Syringe driver:** see syringe driver compatibility chart.

**Mechanism of action:** in nausea and vomiting is through blockade of dopamine receptors in the chemo-receptor trigger zone (CTZ) thus blocking input into the vomiting centre.

**Onset:** of action SC: 10–15 minutes; *Oral*: around 1 hour.

**Peak:** of action SC: 20 minutes; *Oral*: 2–6 hours.

**Duration:** of action initially 8 to 12 hours, maybe up to 24 hours once stable.

**Availability:**

*Tablets (scored):*

0.5mg, PBS general benefit [100](5)

1.5mg, PBS general benefit [100](5)

5mg, PBS general benefit [50](5)

*Oral liquid:*

2mg/mL 100mL, PBS general benefit [1](5)

*Injection:*

5mg/mL 1mL, PBS general benefit [10](0)

*Depot injection:*

50mg/mL 1mL & 3mL, PBS general benefit [5](0)

**Notes:**

- useful as an antiemetic where the causes of nausea and vomiting are biochemical imbalance or toxins.
- particularly useful in opioid induced nausea and vomiting.

## **HEPARIN**

- See Enoxaparin.

## **HYDROGEN PEROXIDE**

*Peroxyl® and extemporaneous preparations*

**Class:** Oxidising agent with antiseptic, deodorant and haemostatic effects.

**Licensed indications:** relief of minor gum and mouth irritation (Peroxy<sup>®</sup>), no licensed indications when extemporaneously prepared.

**Recognised other use(s) in palliative care:** all other uses.

**Contraindications/cautions:** none reported with method of use and concentration used here.

### **Specific considerations:**

*Hepatic impairment:* not reported to require change in use.

*Renal impairment:* not reported to require change in use.

### **Adverse reactions:**

Generally well tolerated when used as mouthwash at concentration of 1.5%.

*Less common:* (rarely seen with low concentrations) mouth ulceration, mucosal irritation, erythema, sloughing, long-term exposure may cause inflammation or hyperplasia e.g. reversible hypertrophy of the papillae of the tongue.

**Interactions:** none reported as not ingested.

### **Dosage:**

*1.5% Solution:* 10mL (undiluted) swilled around the buccal cavity for around 30 seconds and then expelled, use after meals and at bedtime.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** hydrogen peroxide is an oxidising agent, which releases oxygen when applied to tissues. It has weak antibacterial and antiviral activity (including against HIV) and also has deodorant and mild haemostatic actions. The antimicrobial effect of liberated oxygen is reduced in the presence of organic matter.

**Onset:** of action almost immediate.

**Peak:** not applicable.

**Duration:** not applicable.

### **Availability:**

*Mouthwash:* 1.5%

Hydrogen Peroxide 1.5% mouthwash is available as a commercial preparation (Peroxy<sup>®</sup>) or is prepared extemporaneously by a 50:50 dilution of 3% solution immediately prior to use.

PBS notes: Not PBS funded.

**Notes:** none.

## HYDROMORPHONE

Dilaudid®, Dilaudid-HP®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid.

**Licensed indications:** severe pain (more effective in nociceptive than in neuropathic/visceral pain).

**Recognised other use(s) in palliative care:** dyspnoea, cough, diarrhoea.

**Contraindications/cautions:** proven allergy to hydromorphone. Note: past nausea or hallucinations with opioids are not contraindications.

### **Specific considerations:**

*Hepatic impairment:* dose adjustment may be required in hepatic impairment.

Reduce dose and titrate carefully in severe hepatic disease as may precipitate coma.

*Renal impairment:* psychomimetic effects may occur in renal impairment, monitor for adverse effects and in moderate-to-severe impairment reduce dose if needed.

### **Adverse Reactions:**

All opioids share a common range of adverse effects, although these are dose dependent and affected by circumstances of use. There is however significant variation between individuals in their response to different opioids and the different opioids have metabolites which may add to the adverse effects. Switching (rotating) to another, chemically distinct, opioid may therefore be useful to reduce adverse effects by allowing a wash out of these metabolites and presenting the mu receptors with a "fresh" opioid configuration.

**Common: Constipation occurs in up to 90% of patients on opioids, always ensure there is a bowel control plan with laxatives.** Although hydromorphone may be less constipating than morphine, this increases with continued use. Nausea and vomiting are usually transient in the first few (1-5) days and may require metoclopramide or haloperidol to prevent symptoms. Transient confusion and sedation are also common, if persistent they will necessitate a reduction in the opioid dose or switching to another opioid. Dry mouth, dizziness and visual difficulty (particularly problems with accommodation) are also common.

**Less Common:** respiratory depression (usually only at high doses but does occur in the opioid naive when there is no titration of dosage, naloxone can reverse respiratory depression but will also reverse analgesia), myoclonic jerking, delirium, pruritus.

Respiratory depression is a serious side effect of opioids but is a symptom which is uncommon in Palliative Medicine where titration of opioids to pain or breathlessness is the norm. Respiratory rate reduction is often a late manifestation of opioid toxicity, but sedation is a better indicator and can be monitored by using a sedation score such as:

<b>Sedation Score</b>	
Score	Sedation level
0	wide awake
1	easy to rouse
2	easy to rouse, but cannot stay awake
3	difficult to rouse
With opioids, the aim is to keep sedation to a level of less than 2 on this scale.	

Adverse effects, including respiratory depression, will persist for longer if there has been accumulation of hydromorphone e.g. due to hepatic impairment; extended monitoring may therefore be required.

*Rare:* visual hallucinations, hyperalgesia, biliary/urinary tract spasm, physical dependence (irrelevant in palliative care), SIADH, anaphylaxis, seizure.

**Interactions:**

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

**Dosage:**

*Oral:* initially 0.5-1mg 4 hourly, (older and more frail patients require doses at the lower end of this range), titrated to effect

*SC:* initially 0.25-0.5mg 4 hourly, (older and more frail patients require doses at the lower end of this range), titrated to effect

When given by syringe driver prescribe 1/12 to 1/6 of the total 24 hour dose for breakthrough pain

**Syringe driver:** see syringe driver compatibility chart.

**Mechanism of action:** stimulates mu (and other) opioid receptors in the descending inhibitory pathways of the CNS and elsewhere.

**Onset:** of action *SC:* within 15 minutes; *Oral:* within 30 minutes.

**Peak:** of action around 1 hour.

**Duration:** of action around 3 to 5 hours.

**Availability:**

*Tablets:*

2mg, PBS restricted benefit [20](0)

4mg, PBS restricted benefit [20](0)

8mg, PBS restricted benefit [20](0)

*Oral liquid:*

1mg/mL, 473mL PBS restricted benefit [1](0)

*Injection:*

2mg/mL 1mL, PBS general benefit [5](0),

10mg/mL 1mL & 5mL, PBS general benefit [5](0),

10mg/mL 50mL, PBS general benefit [1](0),

Currently only available as the brands Dilaudid® and Dilaudid-HP®.

PBS notes: restricted to severe disabling pain not responding to non-narcotic analgesics.

**Note:**

- paracetamol and an NSAID are effective co-analgesics when given with opioids such as hydromorphone in the treatment of bone and soft tissue pain.
- there is currently no sustained release preparation of hydromorphone in available in Australia.
- hydromorphone is more soluble than morphine and the smaller volume to provide an equivalent analgesic effect may be an advantage when administering via a syringe driver.
- hydromorphone is renally excreted but its metabolites are less active than those of morphine, therefore it may be more suitable than morphine for patients with impaired renal function.

- the 10mg/mL (Dilaudid-HP®) preparations are highly concentrated solutions intended for use in opioid-tolerant patients, confusion with standard parenteral formulations may result in overdose.

## **HYOSCINE BUTYLBROMIDE**

*Buscopan®*

**Class:** Antispasmodic – anticholinergic (gastrointestinal tract).

**Licensed indications:** gastrointestinal spasm and colic, renal and biliary spasm, as an aid in gastrointestinal radiology and endoscopy.

**Recognised other use(s) in palliative care:** some action as anti-emetic and antisecretory, bladder spasm, intestinal obstruction; administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to hyoscine, megacolon, stenosis, glaucoma, tachycardia, urinary retention.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

*Common:* dry mouth.

*Less common:* urinary retention, tachycardia, visual problems, dizziness, constipation.

**Interactions:**

Effect may be antagonised by stimulant laxatives.

Additive effects with other anticholinergic drugs .

Hyoscine may antagonise prokinetic effects of domperidone or metoclopramide.

**Dosage:**

*Oral:* 10-20mg three to four times a day.

*SC:* usually 40-100mg/24 hours, doses up to 120mg/24 hours may be required for bladder spasm or terminal situations.

**Syringe driver:** see syringe driver compatibility table.

**Mechanism of action:** blocks the effect of acetylcholine on gastrointestinal smooth muscle causing relaxation.

**Onset:** of action *Oral:* 1-2 hours; *SC:* 5-10 minutes.

**Peak:** of action *Oral:* 1-2 hours.

**Duration:** of action around 2 hours; half-life is around 5 to 6 hours.

**Availability:**

*Tablets:*

10mg, Not PBS funded

*Injection:*

20mg/mL 1mL, RPBS benefit, PBS Palliative Care authority [5](3)<sup>1</sup>, [5](0)<sup>2</sup>

Currently only available as the brand Buscopan®

PBS notes:

1. initial supply (for up to 4 months) for palliative care patients where colicky pain is a symptom and continuing supply where consultation with a palliative care specialist or service has occurred (3 repeats).
2. continuing supply for palliative care patients where colicky pain is a symptom (no repeats).

**Notes:**

- may be useful with steroids in intestinal obstruction.

- does not cross the blood-brain barrier therefore does not cause drowsiness or have a central anti-emetic action.
- only 8-10% of an orally administered dose is absorbed.
- can be used in sialorrhoea and “death rattle” (retained secretions), although not as effective as hyoscine hydrobromide or glycopyrronium.

## **HYOSCINE HYDROBROMIDE**

*Kwells®*, *Travacalm®*

**Class:** Anticholinergic – antisecretory.

**Licensed indications:** antisecretory premedication, nausea and vomiting.

**Recognised other use(s) in palliative care:** retained secretions (“death rattle”).

**Contraindications/cautions:** proven allergy to hyoscine, elderly, urinary retention, cardiac disease, glaucoma.

**Specific considerations:**

*Hepatic impairment:* caution advised in hepatic impairment.

*Renal impairment:* caution advised in renal impairment.

**Adverse reactions:**

*Common:* dry mouth, tachycardia, hypotension (especially with morphine).

*Less common:* urinary retention, visual problems, dizziness, constipation, drowsiness, hallucinations (more common in the elderly).

**Interactions:**

Effect may be antagonised by stimulant laxatives.

Additive effects with other anticholinergic drugs.

Hyoscine may antagonise prokinetic effects of domperidone or metoclopramide.

**Dosage:**

*Oral:* 0.3-0.6mg, repeated to maximum of 1.2mg in 24 hours.

*SC:* 0.4-2.4mg/24 hours (usually 0.4-0.8mg stat).

**Syringe driver:** see syringe driver compatibility table.

**Mechanism of action:** blocks the cholinergic receptors in CNS and the GIT.

**Onset:** of action *SL:* 10–15min; *IM:* 3–5min.

**Peak:** of action *SL/SC:* 20–60min; *IM:* 1-2 hours.

**Duration:** of action *SL:* about 4 hours; *IM:* about 8 hours.

**Availability:**

*Tablets (scored):*

0.3mg, Not PBS funded.

*Injection:*

0.4mg/mL, Not PBS funded.

Hyoscine hydrobromide tablet preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- thought to cross the blood brain barrier more easily than hyoscine butylbromide.
- risk of confusion in the elderly is high.

## **IBUPROFEN**

Brufen®, Rafen®

[plus various OTC preparations: Nurofen®, Advil®, Bugesic®, Butalgin®, ProVen®, TriProfen®, Chemist's Own®, Heron Blue Ibuprofen®.]

**Class:** Non-steroidal anti-inflammatory drug (NSAID).

**Licensed indications:** pain associated with arthritis, inflammation, antipyretic.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to ibuprofen, gastro-intestinal ulceration, asthma (in NSAID sensitive patients), cardiac impairment.

**Specific considerations:**

*Hepatic impairment:* use with caution in severe impairment; increased risk of bleeding.

*Renal impairment:* pre-existing renal impairment increases the risk of NSAID-induced renal impairment; increased risk of bleeding. Avoid use in moderate-to-severe renal impairment.

**Adverse reactions:**

*Common:* GI ulceration (more common in the elderly), diarrhoea, indigestion, nausea

*Less common:* dizziness, rash, nephrotoxicity, hepatitis, oedema, hypertension, headache, tinnitus, prolonged bleeding time.

**Interactions:**

Ibuprofen is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

Additive effects with other nephrotoxic drugs.

Ibuprofen may reduce effect of diuretics and antihypertensives.

**Dosage:**

*Oral:* 600-2400mg per day in 3 or 4 divided doses.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** inhibits prostaglandin synthesis through the inhibition of cyclo-oxygenase which is present in both COX-1 and COX-2 forms. Inhibition of COX-1 is associated with impaired gastric cytoprotection and anti-platelet function. Inhibition of COX-2 is associated with anti-inflammatory and analgesic action. Reduction in Glomerular Filtration Rate and renal blood flow is associated with both COX-1 and COX-2 inhibition.

**Onset:** of action about 20 to 30 minutes.

**Peak:** of action about 1 to 2 hours.

**Duration:** of action around 4 to 6 hours; half-life is around 2 hours.

**Availability:**

*Tablets:*

200mg, PBS restricted benefit [100](3)<sup>1</sup>, Palliative Care authority [100](3)<sup>2</sup>, Palliative Care authority [100](0)<sup>3</sup>

400mg, PBS general benefit [30](0), PBS restricted benefit [90](3)<sup>1</sup>, Palliative Care authority [90](3)<sup>2</sup>, Palliative Care authority [90](0)<sup>3</sup>

Ibuprofen preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. chronic arthropathies (including osteoarthritis) with an inflammatory component; bone pain due to malignant disease.
2. initial supply (for up to 4 months) for palliative care patients where severe pain is a problem; continuing supply for palliative care patients where severe pain is a problem, and where consultation with a palliative care specialist or service has occurred.
3. continuing supply for palliative care patients where severe pain is a problem.

**Notes:**

- unless contra-indicated, NSAIDs such as ibuprofen should be given alongside regular full-dose paracetamol to provide optimal effect.
- NSAIDs (with paracetamol as above) are an effective co-analgesic when given with opioids in the treatment of bone and soft tissue pain.
- gastric cytoprotection with a proton pump inhibitor e.g. omeprazole, should be considered routinely for palliative care patients requiring systemic NSAIDs.

## KETAMINE

Ketalar®

**Class:** Anaesthetic.

**Licensed indications:** general anaesthesia.

**Recognised other use(s) in palliative care:** severe pain (at sub anaesthetic doses), administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to ketamine, hypertension, tendency to hallucinations, alcohol abuse, epilepsy.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

*Common:* hallucinations (see notes below), delirium, tachycardia, hypertension.

*Less common:* hypotension, bradycardia, laryngospasm, diplopia, respiratory depression.

**Interactions:**

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

**Dosage:**

*Oral:* specific preparation not available, although injection has been given orally.

*SC:* 50–600mg in 24 hours (initially 0.1–0.5mg/kg/hr).

**Syringe driver:** see syringe driver compatibility chart. The Tasmanian Palliative Care service recommends a standard dilution for ketamine, which is to dilute to 17 ml in a 20 ml syringe (to enable the syringe to fit in the driver).

**Mechanism of action:** in pain thought to act by antagonising N-methyl-D-aspartate (NMDA) receptors in the dorsal horn; also interacts with muscarinic receptors, descending monoaminergic pain pathways, calcium channels and opioid receptors in the brain and spinal cord.

**Onset:** of action *SC:* 15 to 30 minutes; *Oral:* 30 minutes; *IV:* 30 seconds.

**Peak:** of action *SC:* not reported; *Oral:* 30 minutes.

**Duration:** of action *SC:* not reported; *Oral:* 4 to 6 hours; *IV:* 5 to 10 minutes.

**Availability:**

*Injection:*

100mg/mL, 2 mL, Not PBS funded.

Currently only available as the brand Ketalar®.

**Notes:**

- May be useful in “wind-up” phenomenon.
  - Wind-up phenomenon can be described as that pain which has escaped the control of analgesia. It occurs where there has been a loss of orderly neural processing of pain, leading to central sensitisation of pain pathways, which results in a clinical picture of rapidly escalating pain despite a corresponding rapid escalation of opioid. It is often also associated with increasing analgesic side effects.
- in opioid tolerance/intolerance, ketamine may allow a reduction in opioid dose.
- may be useful in neuropathic pain.

- if hallucinations occur, reduce the dose of ketamine and give a benzodiazepine e.g. diazepam 5mg orally, midazolam 5mg SC or haloperidol 2-5mg orally or SC.

## KETOCONAZOLE

Nizoral®

**Class:** Antifungal – imidazole.

**Licensed indications:** fungal infections, systemic and deep infections where other forms of treatment have failed, e.g. blastomycosis, paracoccidiomycosis, histoplasmosis; resistant dermatophyte infections in skin and nails.

**Recognised other use(s) in palliative care:** oral candidiasis; repeated vaginal candidiasis, mucocutaneous candidiasis in immunocompromised people.

**Contraindications/cautions:** proven allergy to ketoconazole - consider possibility of cross-reactivity with other azoles, liver function must be monitored in patients receiving treatment with systemic ketoconazole, use with domperidone contraindicated.

**Specific considerations:**

*Hepatic impairment:* systemic use contraindicated in hepatic disease.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

*Common:* gastrointestinal upset, pruritus.

*Less common:* raised liver enzymes, hepatitis, liver damage (usually if given for more than 14 days), gynaecomastia, blood disorders, headache, dizziness, hypertension, adrenal suppression.

**Interactions:**

Ketoconazole is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate. (see below for effect ketoconazole may have on other drugs).

Absorption and effect of ketoconazole may be decreased by antacids, cimetidine, esomeprazole, omeprazole, pantoprazole and ranitidine.

Disulfiram-like reaction may occur with alcohol.

Ketoconazole is also a potent inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a high risk of clinically significant interactions:

Ketoconazole may inhibit the metabolism and increase the concentration and effect of: alprazolam, amitriptyline, buprenorphine, carbamazepine, dexamethasone, diazepam, domperidone (do not use), fentanyl, methadone, midazolam, nortriptyline, oxybutynin, oxycodone, phenytoin, prednisolone, warfarin and venlafaxine.

**Dosage:**

*Oral:* 200mg once a day for 7 days (may be increased to 400–800mg per day depending on susceptibility of infection).

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** impairs synthesis of ergosterol, increasing the permeability of fungal cell membranes and susceptibility to lytic activity by the host defence system.

**Onset:** of action not reported.

**Peak:** of action not reported; however plasma levels peak around 1-2 hours after oral administration.

**Duration:** of action not reported; however ketoconazole has a biphasic half-life, 2 hours during the first 10 hours and 8 hours thereafter.

**Availability:**

Tablets:

200mg, PBS authority benefit [30](5)<sup>1</sup>, [10](0)<sup>2</sup>

PBS notes:

1. oral candidiasis in severely immunocompromised persons where topical therapy has failed; systemic or deep mycoses where other forms of therapy have failed.
2. symptomatic genital candidiasis recurring after treatment of at least 2 episodes with topical therapy.

**Notes:**

- more hepatotoxic than fluconazole.
- more likely to cause interactions than fluconazole.

# KETOROLAC

Toradol®

**Class:** Non-steroidal anti-inflammatory drug (NSAID).

**Licensed indications:** management of moderate to severe pain related to inflammation and tissue injury, metastatic bone pain.

**Recognised other use(s) in palliative care:** administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to ketorolac, cardiac impairment.

**Specific considerations:**

*Hepatic impairment:* use with caution in severe impairment; increased risk of bleeding.

*Renal impairment:* contraindicated in moderate to severe renal impairment as this increases the half-life of ketorolac and the risk of adverse effects such as acute renal failure; reduce dose in mild impairment.

**Adverse reactions:**

*Common:* injection site pain, gastro-intestinal ulcer, bleeding, perforation.

*Less common:* drowsiness, dizziness, headache, sweating, oedema, renal effects, increased bleeding time, raised LFTs, myocardial infarction, stroke, hypertension, hypersensitivity, visual disturbance.

*Rare:* severe skin reactions, anaphylaxis.

**Interactions:**

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

Additive effects with other nephrotoxic drugs.

Ketorolac may reduce the effect of diuretics and antihypertensives.

**Dosage:**

*Oral:* 10mg 4 to 6 hourly (maximum dose 40mg/24hr).

*SC:* <65 yrs 10-30mg 4-6 hrly, maximum dose 90 mg/24hr; >65 yrs 10-15 mg 4-6 hrly, maximum dose 60 mg/24hr.

**Syringe driver:** see syringe driver compatibility chart. Initially 60mg/24hr, increasing (only for patients <65 years of age and >50kg in weight) if necessary by 15mg/24hr to maximum of 90mg/24hr.

**Mechanism of action:** inhibits prostaglandin synthesis through the inhibition of cyclo-oxygenase which is present in both COX-1 and COX-2 forms. Inhibition of COX-1 is associated with impaired gastric cytoprotection and anti-platelet function. Inhibition of COX-2 is associated with anti-inflammatory and analgesic action. Reduction in Glomerular Filtration Rate and renal blood flow is associated with both COX-1 and COX-2 inhibition.

**Onset:** of action *Oral:* 30 minutes; *SC:* not reported; *IM/IV:* 10-30 minutes.

**Peak:** of action not reported; however peak plasma levels *Oral:* 30 to 60 minutes; absorption after IM or SC injection may be slower than that after oral doses in some individuals.

**Duration:** of action *Oral:* 6 hours; *SC:* not reported; half life reported to be 4 to 7 hours.

**Availability:**

*Tablets:*

10mg, Not PBS funded

*Injection:*

10mg/1mL 1mL, Not PBS funded

30mg/1mL 1mL, Not PBS funded

**Notes:**

- ketorolac is a potent NSAID and the resulting NSAID related adverse effects can be serious, e.g. gastro-intestinal haemorrhage and renal impairment.
- increasing the dose of ketorolac beyond the recommendations in the product information will not provide better efficacy but will result in increasing risk of developing serious adverse effects.
- patients should be warned that ketorolac injections are painful.
- unless contra-indicated, NSAIDs such as ketorolac should be given alongside regular full-dose paracetamol to provide optimal effect.
- NSAIDs (with paracetamol as above) are an effective co-analgesic when given with opioids in the treatment of bone and soft tissue pain.
- gastric cytoprotection with a proton pump inhibitor e.g. omeprazole, should be considered routinely for palliative care patients requiring systemic NSAIDs.
- prolonged exposure of the injection solution to light may produce discolouration and promote precipitation.

## LACTULOSE

Actilax®, Genlac®, Lac-dol®, Lactocur®, Duphalac®

**Class:** Laxative – osmotic.

**Licensed indications:** constipation, hepatic encephalopathy.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to lactulose or galactose, partial or complete intestinal obstruction.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* not reported to require dose adjustment.

**Adverse effects:**

*Common:* flatulence, abdominal discomfort, cramps.

*Infrequent:* diarrhoea, electrolyte imbalances with prolonged or excessive doses.

**Interactions:**

None known.

**Dosage:**

Constipation:

*Oral:* initially 20-30mL daily in 1-2 doses, doses of up to 60mL or more may be necessary; maintenance dosage usually 30mL daily.

Hepatic Encephalopathy (see notes):

*Oral:* 30-45mL every 1-2 hours until laxative effect achieved; then reduce dose to 30-45mL 3-4 times daily, aiming to produce 2-3 soft stools per day.

*Rectal:* (if oral route not possible), dilute 300mL of Lactulose oral liquid with 700mL water or sodium chloride 0.9%; retain enema for 30-60 minutes and repeat every 4–6 hours until oral route is available.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** poorly absorbed, metabolised by colonic bacteria to produce low molecular weight organic acids, which promote the retention of water by an osmotic effect, thus increasing peristaltic activity. Effects in hepatic encephalopathy are thought to result from prevention of ammonia absorption by lowering faecal pH, as well as through the laxative effect.

**Onset:** of action 1 to 3 days.

**Peak:** of action not applicable.

**Duration:** of action not applicable.

**Availability:**

*Oral liquid:*

0.67g/mL 500 mL, PBS restricted benefit [1](5)<sup>1</sup>, Palliative Care authority [1](3)<sup>2</sup>, [1](0)<sup>3</sup>

Lactulose preparations are available from a range of manufacturers and may contain different excipients; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS Notes:

1. hepatic coma or precoma (chronic porto-systemic encephalopathy); constipation in patients with malignant neoplasia.
2. initial supply (for up to 4 months) for palliative care patients where constipation is a problem; continuing supply for palliative care patients where constipation is a

problem and where consultation with a palliative care specialist or service has occurred (3 repeats).

3. continuing supply for palliative care patients where constipation is a problem (no repeats).

**Notes:**

- doses of less than 20ml of lactulose are ineffective in opioid induced constipation.
- lactulose is not appropriate for patients with limited fluid intake, due to risk of painful bloating and colic.
- a systemic review has concluded that there was not enough evidence to determine whether lactulose benefited patients with hepatic encephalopathy.

## **LOPERAMIDE**

*Diacare®*, *Diareze®*, *Harmonise®*, *Imodium®*, *Negastro®*, *Chemists Own Diarrhoea Relief®*, *Gastro-Stop®*, *Lopedium®*.

**Class:** Anti-diarrhoeal – opioid.

**Licensed indications:** diarrhoea (short term treatment), intestinal stoma (to reduce frequency and fluidity of motions).

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to loperamide, diarrhoea due to infection or antibiotics, constipation with overflow, intestinal obstruction, may precipitate toxic megacolon in ulcerative colitis.

**Specific considerations:**

*Hepatic impairment:* use with caution because of reduced first pass metabolism.

*Renal impairment:* no dose adjustment is required for patients with renal impairment.

**Adverse reactions:**

*Common:* flatulence, abdominal pain, bloating.

*Less common:* giddiness, paralytic ileus.

**Interactions:**

Effect may be antagonised by prokinetics e.g. domperidone or metoclopramide.

Absorption of loperamide may be decreased by cholestyramine.

**Dosage:**

*Oral:* 2mg after each loose stool to a maximum of 16mg/24 hours.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:**

Binds to opioid ( $\mu$ ) receptors in GI tract, to work as anti-propulsive anti-diarrhoeal; may also affect cholinergic receptors.

**Onset:** of action usually within 1 hour.

**Peak:** of action after 16 to 24 hours; plasma levels peak after around 5 hours.

**Duration:** of action reported to be up to 3 days; half life around 10 hours.

**Availability:**

*Tablets:* 2mg, Not PBS funded.

*Capsules:* 2mg, PBS general benefit [12](0).

Loperamide preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- May not be of benefit if patient is already taking morphine or another opioid.
- Consider possibility of constipation with overflow before starting loperamide in patients on morphine or another opioid.

## LORAZEPAM

Ativan®

**Class:** Benzodiazepine – anxiolytic.

**Licensed indications:** anxiety, insomnia, premedication.

**Recognised other use(s) in palliative care:** muscle spasm, nausea and vomiting (anxiety related).

**Contraindications/cautions:** proven allergy to lorazepam, avoid sudden withdrawal, respiratory depression, sleep apnoea, myasthenia gravis.

**Specific considerations:**

*Hepatic impairment:* contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present; in mild to moderate impairment use lower doses

*Renal impairment:* increased sensitivity to CNS effects in renal impairment, use a lower dose initially in severe impairment.

**Adverse reactions:**

*Common:* sedation, dizziness.

*Less common:* respiratory depression (high dose), disorientation, depression, disinhibition, amnesia.

**Interactions:**

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

**Dosage:**

*Oral:* 2-3mg daily in 2 to 3 divided doses, adjusted according to response (maximum dose 10mg/24 hours).

**Syringe driver:** not applicable.

**Mechanism of action:** may enhance the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

**Onset:** of action 10 to 30 minutes

**Peak:** of action between 1 and 6 hours, typically 2 hours.

**Duration:** of action typically 6 to 8 hours but maybe up to 72 hours; half-life is in range 10 to 20 hours.

**Availability:**

*Tablets (scored):*

1mg, Not PBS Funded.

2.5mg, Not PBS Funded.

Lorazepam preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- lorazepam is a short acting benzodiazepine.
- lorazepam is not metabolised by the Cytochrome P450 system and therefore less likely to be involved in drug interactions compared to other benzodiazepines.
- theoretically the most appropriate benzodiazepine to use in hepatic impairment.

- see below for comparison with other benzodiazepines and zopiclone.

<b>Pharmacological properties and dose equivalents* for benzodiazepines and zopiclone</b>					
Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## METHADONE

Biodone®, Physeptone®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid.

**Licensed indications:** severe pain, acute or chronic; opioid dependence.

**Recognised other use(s) in palliative care:** anti-tussive (other opioids are however more appropriate).

**Contraindications/cautions:** proven allergy to methadone, wide inter-patient variation in pharmacokinetics, risk of accumulation due to long half life, prolonged QT interval.

**Specific considerations:**

*Hepatic impairment:* dose adjustment may be required in hepatic impairment, reduce dose and titrate carefully in severe hepatic disease as may precipitate coma.

*Renal impairment:* longer dosing interval may be required in renal impairment.

**Adverse reactions:**

**Methadone has a variable half life and can rapidly accumulate causing toxicity.**

**Prescribe with care in the elderly as sedation, confusion and respiratory depression can occur suddenly in previously stable patients.**

All opioids share a common range of adverse effects, although these are dose dependent and affected by circumstances of use. There is however significant variation between individuals in their response to different opioids and the different opioids have metabolites which may add to the adverse effects. Switching (rotating) to another, chemically distinct, opioid may therefore be useful to reduce adverse effects by allowing a wash out of these metabolites and presenting the mu receptors with a "fresh" opioid configuration.

*Common:* **Constipation occurs in up to 90% of patients on opioids, always ensure there is a bowel control plan with laxatives.** Although methadone is less constipating than morphine, this increases with continued use. Nausea and vomiting are usually transient in the first few (1-5) days and may require metoclopramide or haloperidol to prevent symptoms. Transient confusion and sedation are also common, if persistent they will necessitate a reduction in the opioid dose or switching to another opioid. Dry mouth, dizziness and visual difficulty (particularly problems with accommodation) are also common.

*Less Common:* respiratory depression (usually only at high doses but does occur in the opioid naive when there is no titration of dosage, naloxone can reverse respiratory depression but will also reverse analgesia), myoclonic jerking, delirium, pruritus.

Respiratory depression is a serious side effect of opioids but is a symptom which is uncommon in Palliative Medicine where titration of opioids to pain or breathlessness is the norm. Respiratory rate reduction is often a late manifestation of opioid toxicity, but sedation is a better indicator and can be monitored by using a sedation score such as:

<b>Sedation Score</b>	
Score	Sedation level
0	wide awake
1	easy to rouse
2	easy to rouse, but cannot stay awake
3	difficult to rouse
With opioids, the aim is to keep sedation to a level of less than 2 on this scale.	

Adverse effects, including respiratory depression, will persist for a more prolonged period with methadone than with other opioids due to its longer half-life and where there has been accumulation e.g. due to hepatic impairment; continued monitoring for 18 to 24 hours, sometimes longer may be necessary.

Rare: visual hallucinations, hyperalgesia, biliary/urinary tract spasm, physical dependence (irrelevant in palliative care), SIADH, anaphylaxis, seizure.

#### **Interactions:**

Methadone is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of methadone may be increased by some cytochrome inhibitors: e.g. cimetidine, fluconazole, fluoxetine, ketoconazole.

Concentration and effect of methadone may be decreased by some cytochrome inducers: e.g. carbamazepine, dexamethasone, phenobarbitone, phenytoin, and rifampicin.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Additive effects with other drugs that prolong the QT interval, increasing risk of arrhythmias.

**Dosage:** (see notes)

*Oral:* initially 5-10mg 4-6 hourly, then convert to twice daily with specialist advice.

*SC:* 50-75% of oral dose.

**Syringe driver:** See syringe driver compatibility table, if uncertain do NOT mix.

**Mechanism of action:** stimulates mu (and other) opioid receptors in the central nervous system and gastro-intestinal system, also thought to act at N-methyl-D-aspartate (NMDA) receptors.

**Onset:** of action *Oral:* within 30 minutes.

**Peak:** of action *Oral:* around 4 hours.

**Duration:** of action *Oral:* initially 6-8 hours then 22-48 hours on repeat dosing.

#### **Availability:**

*Tablets (scored):*

10mg, PBS restricted benefit [20](0)<sup>1</sup>

*Oral Liquid:*

5mg/mL 200mL, Palliative Care authority [1](2)<sup>2</sup> [1](0)<sup>3</sup>, Section 100<sup>4</sup>

*Injection:*

10mg/mL 1mL, PBS restricted benefit [5](0)<sup>1</sup>

Methadone preparations are available from a range of manufacturers and may contain a variety of excipients; seek further advice in patients with intolerance or hypersensitivity to excipients.

**PBS notes:**

1. severe disabling pain unresponsive to non-narcotic analgesics.
2. initial supply (for up to 3 months) for palliative care patients with chronic severe disabling pain not responding to non-narcotic analgesics; continuing supply (for up to 3 months) for palliative care patients with chronic severe disabling pain not responding to non-narcotic analgesics and where consultation with a palliative care specialist or service has occurred (3 repeats).
3. continuing supply (for up to 1 month) for palliative care patients with chronic severe disabling pain not responding to non-narcotic analgesics (no repeats).
4. treatment of opiate dependence in accordance with State or Territory law.

**Notes:**

- paracetamol and an NSAID are effective co-analgesics when given with opioids such as methadone in the treatment of bone and soft tissue pain.
- methadone may be useful in opioid rotation.
- methadone may be useful in neuropathic pain.
- as methadone affects N-methyl-D-aspartate (NMDA) receptors it may prevent "wind up" phenomenon on long term use.
  - Wind-up phenomenon can be described as that pain which has escaped control of analgesia. It occurs where there has been a loss of orderly neural processing of pain, leading to central sensitisation of pain pathways, which results in a clinical picture of rapidly escalating pain despite a corresponding rapid escalation of opioid. It is often also associated with increasing analgesic side effects.
- although renal or hepatic impairment may be less of a problem with methadone than with some other opioids, it remains essential to titrate the dose and adjust the dosage interval according to response in such patients.
- methadone by subcutaneous injection may be irritable.
- converting patients from morphine requires care as the half life of methadone varies between individuals.
- when converting from morphine stop the morphine and calculate the starting dose as follows:

<b>MORPHINE TO METHADONE CONVERSION</b>		
<b>Daily morphine dose</b>	<b>Conversion ratio</b>	<b>Daily methadone dose</b>
<100mg	3 : 1 (i.e. 3mg morphine : 1mg methadone)	0 to 30mg methadone
101 - 300mg	5 : 1	20 to 60mg methadone
301 - 600mg	10 : 1	30 to 60mg methadone
601 - 800mg	12 : 1	50 to 65mg methadone
801 - 1000mg	15 : 1	50 to 65mg methadone
>1000mg	20 : 1	50mg methadone

Adapted from Ayonrinde & Bridge, MJA, 2000

- on day one give a "loading dose" of 25-50% greater than that obtained from the conversion ratio above, give this in four divided doses over 24 hours.
- reduce this dose over next two days titrating to pain, convert to twice daily dosing after three to five days.
- prescribe morphine or another opioid (in immediate release form) for breakthrough pain.

## **METHOTRIMEPRAZINE (LEVOMEPRMAZINE)**

Nozinan®

**Class:** Phenothiazine - antipsychotic/neuroleptic.

**Licensed indications:** psychosis, terminal pain with restlessness and distress, delirium.

**Recognised other use(s) in palliative care:** nausea and vomiting, pain.

**Contraindications/cautions:** proven allergy to methotrimeprazine - consider possibility of cross-sensitivity with other phenothiazines, Parkinson's Disease.

**Specific considerations:**

*Hepatic impairment:* phenothiazines are hepatotoxic and may precipitate coma.

*Renal impairment:* start with small dose in severe renal impairment.

**Adverse reactions:**

*Common:* somnolence, postural hypotension, sedation.

*Less common:* dry mouth, hypotension, extra pyramidal side-effects (usually with long term high dose use), prolongation of the QT interval.

**Interactions:**

Methotrimeprazine (and its metabolites) may inhibit the Cytochrome P450 system involved in the metabolism of other drugs. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other CNS depressant drugs.

Additive effects with other drugs that prolong the QT interval, increasing the risk of arrhythmias.

**Dosage:**

Nausea/vomiting:

*Oral:* 6.25-12.5mg daily.

*SC:* 6.25-12.5mg daily.

Pain, restlessness, distress, delirium:

*Oral:* 6.25-50mg every 4 to 8 hours.

*SC:* 5-200mg/24 hours (doses < 25 mg associated with less sedation).

**Syringe driver:** see syringe driver compatibility table, preferably use 0.9% sodium chloride as the diluent.

**Mechanism of action:** suppresses sensory impulses in the CNS mediated via various neurotransmitters including 5 hydroxy-tryptamine (5HT).

**Onset:** of action *Oral* / *SC:* 20 to 40 minutes.

**Peak:** of action *Oral:* 1 to 4 hours; *SC:* 30 to 90 minutes.

**Duration:** of action *Oral* / *SC:* 12 to 24 hours; half-life reported to be 15 to 30 hours.

**Availability:**

*Tablets:*

25mg, Not PBS funded, available through Special Access Scheme (SAS).

100mg, Not PBS funded, available through Special Access Scheme (SAS).

*Injection:*

25mg/mL, 1mL, Not PBS funded, available through Special Access Scheme (SAS).

**Notes:**

- methotrimeprazine is the only phenothiazine with analgesic properties.

- benztropine may be useful in alleviating extra pyramidal side-effects.

## **METHYLPHENIDATE**

*Attenta®*, *Ritalin®*, *Concerta®*

**Class:** CNS stimulant - amphetamine related.

**Licensed indications:** attention deficit hyperactivity disorder (ADHD), narcolepsy.

**Recognised other use(s) in palliative care:** depression, neurobehavioral symptoms in brain tumours/injuries, dementia, reversal of opioid induced somnolence, short term reversal of fatigue.

**Contraindications/cautions:** proven allergy to methylphenidate, anxiety, glaucoma, agitation, hyperthyroidism, cardiac problems, hypertension, epilepsy.

**Specific considerations:**

*Hepatic impairment:* halve dose in severe impairment.

*Renal impairment:* renal insufficiency is expected to have little effect on pharmacokinetics of methylphenidate.

**Adverse reactions:**

*Common:* nervousness, insomnia, tachycardia, urticaria.

*Less common:* blurred vision, hallucinations, blood disorders, psychosis (very high doses), arrhythmias.

**Interactions:**

Methylphenidate may be metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of methylphenidate may be increased by some cytochrome inhibitors: e.g. valproate.

Concentration and effect of methylphenidate may be decreased by some cytochrome inducers: e.g. carbamazepine.

Methylphenidate is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Methylphenidate may inhibit the metabolism and increase the concentration and effect of: amitriptyline, nortriptyline, phenobarbitone, phenytoin, warfarin.

Methylphenidate may increase risk of dyskinesias with risperidone.

Methylphenidate may enhance analgesic effect and decrease sedation with opioids.

Methylphenidate may cause hypertension with tricyclic antidepressants.

**Dosage:**

Depression:

*Oral (standard tablets):* 10-30mg per day (give in two divided doses, first dose in morning and second dose at mid-day) adjusted according to response, occasionally higher doses may be required (maximum dose 1mg/kg/24 hours).

*Oral (CR tablets):* not usually used in palliative care.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** acts as a stimulant in the CNS through enhancement of noradrenergic and dopaminergic neurotransmission.

**Onset:** of action in depression 2 to 5 days.

**Peak:** of action not reported; however plasma levels peak 1 to 2 hours after dosing with standard tablets.

**Duration:** of action 3 to 6 hours for standard tablets.

**Availability:**

Tablets:

10mg, PBS authority benefit [100](5)<sup>1,3</sup>

Tablets (controlled release):

18mg, PBS authority benefit [30](5)<sup>2,3</sup>

27mg, PBS authority benefit [30](5)<sup>2,3</sup>

36mg, PBS authority benefit [30](5)<sup>2,3</sup>

54mg, PBS authority benefit [30](5)<sup>2,3</sup>

Capsules (controlled release):

20mg, PBS authority benefit [30](5)<sup>2,3</sup>

30mg, PBS authority benefit [30](5)<sup>2,3</sup>

40mg, PBS authority benefit [30](5)<sup>2,3</sup>

Methylphenidate preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. use in attention deficit hyperactivity disorder, in accordance with State/Territory law.
2. treatment of attention deficit hyperactivity disorder (ADHD) in a patient aged 6 to 18 years inclusive, who has demonstrated a response to immediate release methylphenidate hydrochloride with no emergence of serious adverse events, and who requires continuous coverage over 12 hours.
3. separate Authorisation is required from the Tasmanian Chief Pharmacist for prescription in Tasmania.

**Notes:** none.

## **METOCLOPRAMIDE**

*Maxolon®*, *Pramin®*

**Class:** Antiemetic – prokinetic, dopamine antagonist.

**Licensed indications:** nausea, vomiting, gastric stasis, aid in radiological procedures, difficult intestinal intubation.

**Unlicensed use:** gastro-oesophageal reflux disease, hiccoughs, stimulation of lactation, relief of migraine (in combination with analgesics).

**Contraindications/cautions:** proven allergy to metoclopramide, complete intestinal obstruction, pheochromocytoma, younger and older persons more prone to extra pyramidal side-effects.

### **Specific considerations:**

*Hepatic impairment:* caution may be required, although no dose adjustment is routinely recommended for patients with hepatic impairment.

*Renal impairment:* reduce dose in moderate and severe renal impairment; extra-pyramidal side-effects are more common.

### **Adverse reactions:**

*Common:* restlessness, drowsiness, dizziness, headache.

*Less common:* tardive dyskinesia – usually on prolonged use, extra pyramidal reactions e.g. parkinsonism, akathisia (usually at doses >30mg/24 hours, consider switch to domperidone which has less central effects), diarrhoea, restlessness.

### **Interactions:**

Prokinetic effect of metoclopramide may be reduced by opioids.

Prokinetic effect of metoclopramide may be reduced by anticholinergics e.g. hyoscine.

Combination of IV metoclopramide and IV ondansetron has been associated with an increased risk of cardiac arrhythmias.

Metoclopramide may increase the rate of onset of action of SR morphine.

Metoclopramide may increase absorption of paracetamol.

### **Dosage:**

*Oral:* 10mg up to three times a day.

*SC:* 30–60mg over 24 hours (be particularly alert for extra pyramidal effects at doses >30 mg/24 hours).

**Syringe driver:** see syringe driver compatibility table.

**Mechanism of action:** blocks dopamine receptors in the gastrointestinal tract (increasing peristalsis), the CNS and the chemoreceptor-trigger zone (CTZ).

**Onset:** of action *Oral:* 15 to 60 minutes.

**Peak effect:** of action *Oral:* 1 to 3 hours.

**Duration:** of action not reported; however plasma half-life 2.5 to 6 hours.

### **Availability:**

*Tablets (scored):*

10mg, PBS general benefit [25](0)

*Injection:*

5mg/mL 2 mL, PBS general benefit [10](0)

Metoclopramide preparations are available from a variety of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- “high dose metoclopramide” may work via 5HT<sub>3</sub> antagonism (as with ondansetron) but is associated with severe extra pyramidal effects.
- most effective for nausea and/or vomiting due to gastric stasis.

## **METRONIDAZOLE**

Flagyl® , Metrogyl® , Metronide® , Rozex®

**Class:** Antibiotic – anti-anaerobic and anti-protozoal.

**Licensed indications:** Gram-positive and Gram-negative anaerobic bacterial infections; Protozoal infections; *Clostridium difficile*-associated disease; dental infections, including acute gingivitis; intra-abdominal infections; aspiration pneumonia; lung abscess; bacterial vaginosis; pelvic inflammatory disease; amoebiasis; surgical prophylaxis; eradication of *H. Pylori* infections (as part of a multidrug regimen); rosacea.

**Recognised other use(s) in palliative care:** useful in controlling malodorous wounds.

**Contraindications/cautions:** proven allergy to metronidazole or tinidazole.

**Specific considerations:**

*Hepatic impairment:* reduce dosage in severe hepatic impairment due to risk of drug accumulation and toxicity.

*Renal impairment:* metabolites may accumulate in severe renal impairment possibly causing adverse effects, however dose adjustment is not usually necessary.

**Adverse reactions:**

*Common:* gastro-intestinal upset, urticaria, metallic taste, furry tongue.

*Less common:* drowsiness, headache, dizziness, darkening of urine.

**Interactions:**

Metronidazole is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of metronidazole may be increased by some cytochrome inhibitors: e.g. cimetidine.

Concentration and effect of metronidazole may be decreased by some cytochrome inducers: e.g. phenobarbitone.

Disulfiram-like reaction when alcohol combined with metronidazole.

Metronidazole is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Metronidazole may inhibit the metabolism and increase the concentration and effect of: carbamazepine, phenytoin, warfarin.

**Dosage:**

*Oral:* 400mg three times a day.

*SC:* not used.

*IV infusion:* 500mg three times a day.

*Rectal:* 1g three times a day for 3 days then twice a day.

*Topical:* apply twice a day.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** thought to be reduced by bacterial enzymes to a metabolite which interferes with DNA, effectively preventing further bacterial replication and leading to bacterial death.

**Onset:** of action not reported.

**Peak:** of action not reported; however peak plasma levels *Oral:* 1 to 2 hours; *Rectal:* 5 to 12 hours.

**Duration:** of action reported to be 8 to 12 hours; half-life 6 to 11 hours.

**Availability:**

*Tablets (scored):*

200mg, PBS general benefit [21](1)

400mg, PBS general benefit [5](2), PBS restricted benefit [21](1)<sup>1</sup>

*Oral liquid:*

40mg/mL 100 mL, PBS general benefit [1](0)

*Injection:*

5mg/mL 100 mL, PBS restricted benefit [5](1)<sup>2</sup>

*Suppositories:*

500mg 10, PBS general benefit [1](0)

*Topical gel:*

0.5%, Not PBS funded

0.75%, Not PBS funded

Metronidazole preparations are available from a range of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. restricted benefit for treatment of anaerobic infections.
2. restricted benefit for prophylaxis in large bowel surgery; treatment in a hospital of acute anaerobic sepsis.

**Notes:** none.

## **MEXILETINE**

Mexitil®

**Class:** Antiarrhythmic - orally active lignocaine analogue.

**Licensed indications:** prevention of serious ventricular arrhythmias.

**Recognised other use(s) in palliative care:** neuropathic pain.

**Contraindications/cautions:** proven allergy to mexiletine, recent myocardial infarction, decreased cardiac output.

**Specific considerations:**

*Hepatic impairment:* in severe hepatic impairment reduce dose according to plasma concentration (see notes).

*Renal impairment:* in severe renal impairment reduce dose according to plasma concentration (see notes).

**Adverse reactions:**

*Common:* nausea, vomiting, constipation, dizziness, blurred vision.

*Less common:* cardiac arrhythmias, hypotension, Stevens-Johnson syndrome, erythroderma, blood dyscrasias, abnormal LFTs, hepatic necrosis, cardiac arrest.

**Interactions:**

Mexiletine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs affecting this system:

Concentration and effect of mexiletine may be decreased by some cytochrome inducers: e.g. phenytoin and rifampicin.

Additive effects with other drugs that prolong the QT interval, increasing the risk of arrhythmias.

Absorption may be affected by opioids or prokinetics.

**Dosage:**

Pain (specialist advice recommended):

*Oral:* initially 50mg three times a day, increasing gradually every 3 to 7 days according to response and tolerability, up to a maximum of 300mg three times a day.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** in pain thought to decrease excitability of nerve cells.

**Onset:** of action for arrhythmias typically 1 to 3 hours, maybe longer for pain.

**Peak:** of action not reported; however peak plasma levels occur after 2 to 3 hours.

**Duration:** of action typically 6 to 8 hours; half-life ranges from 5 to 17 hours.

**Availability:**

*Capsules:*

50mg, PBS general benefit [100](5)

200mg, PBS general benefit [100](5)

Currently only available as the brand Mexitil®.

**Notes:**

- seek specialist advice before prescribing mexiletine.
- normal therapeutic range for mexiletine is 0.5–2mg/L.

# MICONAZOLE

Daktarin®

**Class:** Antifungal – imidazole.

**Licensed indications:** fungal infection: topical, oral, gastro-intestinal, vaginal.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to miconazole - consider possibility of cross-sensitivity with other azoles.

**Specific considerations:**

*Hepatic impairment:* contra-indicated in hepatic dysfunction.

*Renal impairment:* doses may need to be reduced in renal impairment.

**Adverse reactions:**

*Common:* oral gel - GI upset.

*Less common:* oral gel - hepatitis, topical/vaginal– burning, itching.

**Interactions:**

Note: miconazole is systemically absorbed from the oral gel with risk of interactions.

Miconazole is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate (see below for effect miconazole may have on other drugs).

Miconazole is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs and where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Miconazole may inhibit the metabolism and increase the concentration and effect of: alprazolam, amitriptyline, carbamazepine, midazolam, nortriptyline, phenytoin, warfarin.

**Dosage:**

*Topical oral:* half a spoonful using measure provided four times daily for 7 to 14 days.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** impairs synthesis of ergosterol, increasing permeability of fungal cell membrane and susceptibility to lytic activity by the host defence system.

**Onset:** of action within 24 hours for treatment of oral candidiasis.

**Peak:** of action not reported; however peak plasma levels usually around 2 hours after oral (topical) use.

**Duration:** of action not reported; however half-life around 24 hours.

**Availability:**

*Oral gel:* 20mg/mL, 15 & 40 g, Not PBS funded

*Various other preparations:* Not usually applicable in palliative care.

**Notes:** miconazole is systemically absorbed from the oral gel.

## **MICROLAX®**

(Sodium citrate, sodium laurylsulphoacetate, sorbitol, sorbic acid)

**Class:** Laxative – rectal, stimulant, faecal softener and osmotic.

**Licensed indications:** constipation, bowel evacuation.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to constituents, rectal perforations have occurred with enemas therefore care required during administration.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* not reported to require dose adjustment.

**Adverse effects:**

*Common:* rectal irritation.

*Less common:* excessive use may cause diarrhoea and fluid loss.

**Interactions:** none reported.

**Dosage:**

*Rectal:* contents of one tube used as required.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** multiple effects, may stimulate colonic activity via nerves in the intestinal mucosa and increase the uptake of fluid by stools thus softening them.

**Onset:** of action usually within 5 to 15 minutes.

**Peak:** of action usually within 15 minutes.

**Duration:** of action not applicable.

**Availability:**

*Enema:*

5mL, PBS restricted benefit [24](2)<sup>1</sup>, RPBS benefit [4](0), Palliative Care authority [24](3)<sup>2</sup> [24](0)<sup>3</sup>,

PBS notes:

1. paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function; patients who are receiving long-term nursing care on account of age, infirmity or other condition in hospitals, nursing homes or residential facilities; for use by a patient who is receiving long-term nursing care and in respect of whom a Carer Allowance is payable as a disabled adult; patients receiving palliative care; terminal malignant neoplasia; anorectal congenital abnormalities; megacolon.
2. initial supply (for up to 4 months) for palliative care patients where constipation is a problem; continuing supply for palliative care patients where constipation is a problem, and where consultation with a palliative care specialist or service has occurred.
3. continuing supply for palliative care patients where constipation a problem.
4. **Notes:** none.

## MIDAZOLAM

Hypnovel®

**Class:** Benzodiazepine – sedative.

**Licensed indications:** adjunctive treatment for epilepsy refractory to other antiepileptic drugs, in particular absence and myoclonic seizures, and infantile spasms; acute treatment of seizures, including status epilepticus; anaesthetic induction agent.

**Recognised other use(s) in palliative care:** sedation, terminal restlessness, hiccoughs, epilepsy, muscle spasm, dyspnoea; administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to midazolam, avoid sudden withdrawal, respiratory depression.

### **Specific considerations:**

*Hepatic impairment:* increased sensitivity to CNS effects, avoid in severe hepatic impairment as can precipitate coma.

*Renal impairment:* increased sensitivity to CNS effects, reduce dose in severe renal impairment.

### **Adverse reactions:**

*Common:* fatigue, drowsiness, amnesia.

*Less common:* respiratory depression (high dose), aggression, confusion, hypotension.

### **Interactions:**

Midazolam is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of midazolam may be increased by cytochrome inhibitors: e.g. cimetidine, fluconazole, fluoxetine, ketoconazole, miconazole, valproate.

Concentration and effect of midazolam may be decreased by cytochrome inducers: e.g. carbamazepine, dexamethasone, phenytoin, rifampicin, tobacco smoke.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

### **Dosage:**

SC: 5-60mg/24 hours. If not effective at doses around 60mg/24 hours, seek specialist advice regarding available options which may include adding another drug.

**Syringe driver:** see syringe driver compatibility table.

**Mechanism of action:** may enhance the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

**Onset:** of action *Buccal:* 15 minutes; *SC:* 5–10min; *IV:* 2–3min.

**Peak:** of action not reported; however peak plasma levels *Buccal:* 30min; *IM:* 30min.

**Duration:** of action variable from 15 minutes to several hours, half-life 2 to 5 hours.

### **Availability:**

*Injection:*

1 mg/mL 5mL, Non PBS funded

5mg/mL 1mL, Non PBS funded

5mg/mL 3mL, Non PBS funded

5mg/mL 10mL, Non PBS funded

Midazolam preparations are available from a range of manufacturers and may contain a variety of excipients; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- midazolam is a very short acting benzodiazepine so dose titration to response is easier than with longer acting benzodiazepines e.g. clonazepam.
- IV administration can result in hypotension and transient apnoea.
- benzodiazepines may reduce dyspnoea by anxiolytic and sedative effects.
- in renal failure a metabolite of midazolam can accumulate to cause paradoxical restless and confusion.
- see below for comparison with other benzodiazepines and zopiclone.

<b>Pharmacological properties and dose equivalents* for benzodiazepines and zopiclone</b>					
Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## MIRTAZAPINE

Avanza®, Mirtazon®, Remeron®, Axit®

**Class:** Antidepressant – presynaptic alpha-2 adrenergic receptor antagonist.

**Licensed indications:** major depressive illness.

**Recognised other use(s) in palliative care:** adjunct to pain management.

**Contraindications/cautions:** proven allergy to mirtazapine or mianserin, treatment with or within 14 days of stopping an MAOI, epilepsy, bipolar disorder.

### **Specific considerations:**

*Hepatic impairment:* careful dosing as well as regular and close monitoring is necessary in patients with hepatic insufficiency.

*Renal impairment:* careful dosing as well as regular and close monitoring is necessary in patients with renal insufficiency.

### **Adverse effects:**

*Common:* increased appetite, weight gain, sedation, weakness, peripheral oedema

*Rare:* orthostatic hypotension, seizures, mania, rash, granulocytosis, eosinophilia.

### **Interactions:**

Mirtazapine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of mirtazapine may be increased by cytochrome inhibitors:  
e.g. cimetidine, fluconazole, ketoconazole.

Concentration and effect of mirtazapine may be decreased by cytochrome inducers:  
e.g. carbamazepine, phenytoin, rifampicin.

Additive effects with other CNS depressant drugs.

Additive effects with other serotonergic drugs, increasing risk of serotonin syndrome.

Mirtazapine is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, however its effects are reported to be weak; therefore the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate (see above for effect other drugs may have on mirtazapine).

### **Dosage:**

*Oral:* 7.5-15 mg at night, increasing gradually as required to usual maintenance dose of 30–45mg at night, maximum 60mg per day.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** acts as a presynaptic alpha-2 adrenergic receptor antagonist, which increases central noradrenergic and serotonergic neurotransmission.

**Onset:** of action in depression 2 to 4 weeks, maybe more rapid in other indications.

**Peak:** of action not reported; however plasma levels peak after about 2 hours.

**Duration:** of action not reported; however mean half-life ranges from 20 to 40 hours.

### **Availability:**

*Tablets (scored):*

30mg, PBS restricted benefit [30](5)<sup>1</sup>

45mg, PBS restricted benefit [30](5)<sup>1</sup>

*Wafer:*

15mg, PBS restricted benefit [30](5)<sup>1</sup>

30mg, PBS restricted benefit [30](5)<sup>1</sup>

45mg, PBS restricted benefit [30](5)<sup>1</sup>

Mirtazapine preparations are available from a range of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. restricted benefit for major depressive illness.

**Notes:** none

## MORPHINE

Sevredol®, Anamorph®, Ordine®, MS Contin®, Kapanol®, MS Mono®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid.

**Licensed indications:** moderate to severe acute or chronic pain (more effective in nociceptive than in neuropathic/visceral pains), adjunct during general anaesthesia.

**Recognised other use(s) in palliative care:** severe breathlessness, acute pulmonary oedema, cough, diarrhoea.

**Contraindications/cautions:** proven allergy to morphine or codeine. Note: past nausea or hallucinations with opioids are not contraindications.

### **Specific Considerations:**

*Hepatic impairment:* doses should be reduced in mild to moderate impairment; avoid in severe hepatic impairment, may cause excessive sedation or coma.

*Renal impairment:* chronic use in moderate renal impairment requires lower doses; taking into account adverse effects and need for adequate analgesia. Reduce dose in severe renal impairment and avoid chronic use as active metabolites accumulate.

*Route of administration:* the route of administration influences the rate of accumulation of morphine metabolites, subcutaneous administration produces less metabolites than the oral route because of the avoidance of “first pass” metabolism.

### **Adverse reactions:**

All opioids share a common range of adverse effects, although these are dose dependent and affected by circumstances of use. There is however significant variation between individuals in their response to different opioids and the different opioids have metabolites which may add to the adverse effects. Switching (rotating) to another, chemically distinct, opioid may therefore be useful to reduce adverse effects by allowing a wash out of these metabolites and presenting the mu receptors with a "fresh" opioid configuration.

*Common:* **Constipation occurs in up to 90% of patients on opioids, always ensure there is a bowel control plan with laxatives.** Morphine is probably the most constipating opioid and this increases with continued use. Nausea and vomiting are usually transient in the first few (1-5) days and may require metoclopramide or haloperidol to prevent symptoms. Transient confusion and sedation are also common, if persistent they will necessitate a reduction in the opioid dose or switching to another opioid. Dry mouth, dizziness and visual difficulty (particularly problems with accommodation) are also common.

*Less Common:* respiratory depression (usually only at high doses but does occur in the opioid naive when there is no titration of dosage, naloxone can reverse respiratory depression but will also reverse analgesia), myoclonic jerking, delirium, pruritus.

Respiratory depression is a serious side effect of opioids but is a symptom which is uncommon in Palliative Medicine where titration of opioids to pain or breathlessness is the norm. Respiratory rate reduction is often a late manifestation of opioid toxicity, but sedation is a better indicator and can be monitored by using a sedation score such as:

<b>Sedation Score</b>	
Score	Sedation level
0	wide awake
1	easy to rouse
2	easy to rouse, but cannot stay awake
3	difficult to rouse
With opioids, the aim is to keep sedation to a level of less than 2 on this scale.	

Adverse effects, including respiratory depression, will persist for longer if there has been accumulation of morphine (e.g. due to hepatic or renal impairment) or where modified-release preparations have been used; extended monitoring may therefore be required.

Rare: visual hallucinations, hyperalgesia, biliary/urinary tract spasm, physical dependence (irrelevant in palliative care), SIADH, anaphylaxis, seizure.

#### **Interactions:**

Rifampicin may decrease concentration and effect of morphine.

Metoclopramide may increase the rate of onset of action of SR morphine.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Pro-kinetic effect of domperidone and metoclopramide antagonised by opioids.

#### **Dosage:**

Pain: dosage depends on whether the patient is opioid naive or already on opioids.

**Opioid naive: It is not recommended to start opioid naive patients on a controlled release (sustained-release / long-acting) morphine preparation, such patients should be titrated to effect with normal release tablets or liquid initially.**

*Oral:* Initially 2.5–5 mg (normal release) every 4 hours, titrated to effect.

**Already on opioid: Initial dose should be dependent on previous opioid exposure, it is recommended to start with an equianalgesic dose of morphine normal release tablets or liquid and titrate to effect.**

When stable and appropriate to convert to controlled release morphine: half the total 24 hour dose (as determined by titration), may be given every 12 hours as MS Contin or Kapanol; or the total 24 hour dose may be given as MS Mono (There is some evidence to suggest that Kapanol can be given as a single 24 hour dose in some circumstances). Rescue doses of 1/12th or 1/6th of the total 24 hour dose should always be prescribed so they are available to manage occasional breakthrough pain.

Note: although there is no real maximum dose, morphine doses are typically less than 200mg/24 hours. Doses of >200mg/24 hours should trigger a review and consideration of a neuropathic component to the pain, with the analgesic regime modified accordingly.

SC: the dose should be based on the existing oral dose and an oral : SC dosing ratio of 3 : 1, i.e. 30mg oral morphine = 10mg subcutaneous morphine.

Breathlessness, cough:

*Oral:* 5–10mg (normal release) 4 hourly.

**Syringe driver:** see syringe driver compatibility table.

**Mechanism of action:** stimulates mu (and other) opioid receptors in the descending inhibitory pathways of the CNS and in the GIT. Cough suppression occurs through effects in the medullary centre of the brain.

**Onset:** of action *Oral (normal release): within 30 minutes*

**Peak:** of action *Oral (normal release): 1 hour; IM: 30 to 60 minutes; SC: 5 to 90 minutes.*

**Duration:** of action *Oral (normal release) / SC:* 4 to 5 hours (takes approximately 6 cycles of the drug to reach steady state); *Oral (controlled release):* 8 to 12 hours (Note: Kapanol may be longer and MS Mono is said to have a 24 hour action).

**Availability:**

*Tablets (normal release, scored):*

10mg, Palliative care benefit [20](2)<sup>3</sup> [20](0)<sup>4</sup>

20mg, Palliative care benefit [20](2)<sup>3</sup>, [20](0)<sup>4</sup>

30mg, PBS restricted benefit [20](0)<sup>5</sup>

*Tablets (controlled release):*

5mg, PBS restricted benefit [20](0)<sup>1</sup>

10mg, PBS restricted benefit [20](0)<sup>1</sup>

15mg, PBS restricted benefit [20](0)<sup>1</sup>

30mg PBS restricted benefit [20](0)<sup>1</sup>

60mg, PBS restricted benefit [20](0)<sup>1</sup>

100mg PBS restricted benefit [20](0)<sup>1</sup>

200mg, PBS restricted benefit [20](0)<sup>2</sup>, Palliative Care authority [20](2)<sup>3</sup>, [20](0)<sup>4</sup>, RPBS benefit [20](0)<sup>5</sup>

*Capsules (controlled release)*

10mg, PBS restricted benefit [20](0)<sup>1</sup>

20mg, PBS restricted benefit [20](0)<sup>1</sup>

30mg, PBS restricted benefit [10](0)<sup>1</sup>

50mg, PBS restricted benefit [20](0)<sup>1</sup>

60mg, PBS restricted benefit [10](0)<sup>1</sup>

90mg, PBS restricted benefit [10](0)<sup>1</sup>

100mg, PBS restricted benefit [20](0)<sup>1</sup>

120mg, PBS restricted benefit [10](0)<sup>1</sup>

*Oral liquid*

1mg/mL 200 mL, Not PBS funded

2mg/mL 200 mL, PBS restricted benefit [1](0)<sup>5</sup>

5mg/mL 200 mL, PBS restricted benefit [1](0)<sup>5</sup>

10mg/mL 200 mL, PBS restricted benefit [1](0)<sup>5</sup>

*Sachets (controlled release, granules)*

30mg, PBS restricted benefit [20](0)<sup>1</sup>

60mg, PBS restricted benefit [20](0)<sup>1</sup>

100mg, PBS restricted benefit [20](0)<sup>1</sup>

200mg, PBS restricted benefit [20](0)<sup>1</sup>

*Injection:*

5mg/mL 1mL, Not PBS funded

10mg/mL 1mL, PBS general benefit

15mg/mL 1mL, PBS general benefit

30mg/mL 1mL, PBS general benefit

80mg/mL 1.5mL, PBS general benefit

80mg/mL 5mL, Not PBS funded

Morphine preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. chronic severe disabling pain not responding to non-narcotic analgesics.
2. chronic severe disabling pain due to cancer.
3. initial supply (for up to 3 months) for palliative care patients with severe disabling pain not responding to non-narcotic analgesics; continuing supply (for up to 3 months) for palliative care patients with severe disabling pain not responding to non-narcotic analgesics, and where consultation with a palliative care specialist or service has occurred.
4. continuing supply (for up to 1 month) for palliative care patients with chronic severe disabling pain not responding to non-narcotic analgesics.
5. severe disabling pain not responding to non-narcotic analgesics.

**Notes:**

- paracetamol and an NSAID are effective co-analgesics when given with opioids such as morphine in the treatment of bone and soft tissue pain.
- tolerance to the effect of morphine is rare, disease progression is the most likely cause of dose fade.
- rectal absorption of morphine is unreliable and this is not a preferred route, although MS Contin oral tablets can be given rectally if appropriate.
- Kapanol capsules can be opened and sprinkled on food or given via a PEG or nasogastric tube.
- for conversion to fentanyl or methadone see fentanyl or methadone pages.
- toxicity indicated by sedation, confusion, decreased respiratory rate, blood pressure.
- morphine route dose conversion:
  - Oral to SC = 3:1, i.e. 30mg oral = 10mg SC.
  - Oral to rectal = 1:1, i.e. 10mg oral = 10mg rectal.
- the 80mg/mL injection solutions contain morphine tartrate (rather than morphine sulphate), however as morphine tartrate 120mg is approximately equivalent to morphine sulphate 117mg, this has little clinical significance.

## NALOXONE

Naloxone Min-I-Jet®

**Class:** Opioid antagonist.

**Licensed indications:** opioid overdose.

**Recognised other use(s) in palliative care:** enhancement of opioid analgesia and alleviation of side-effects at very low dose (specialist use only).

**Contraindications/cautions:** proven allergy to naloxone, cardiovascular disease.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* not reported to require dose adjustment, however excretion of some opioids and/or their active metabolites is delayed in renal impairment and they may accumulate; extended treatment with naloxone including infusion may therefore be required to maintain reversal of opioid effect in renal impairment.

**Adverse reactions:**

*Common:* nausea, vomiting, tachycardia, sweating, raised blood pressure (due to opioid withdrawal).

**Interactions:**

Naloxone blocks the effects of opioid agonists.

**Dosage:**

If respiratory rate < 8 per minute, patient unconscious or cyanosed:

*IV:* 0.1-0.4mg every 2-3 minutes for reversal of respiratory depression; 0.4-2mg every 2-3 minutes for overdose in opioid dependent patients, up to maximum of 10mg.

*SC:* see below.

**Syringe driver:** not applicable.

**Mechanism of action:** blocks action of opioid agonists at opioid receptors.

**Onset:** of action *IV:* 1-3 minutes, *SC/IM:* 2-15 minutes.

**Peak:** of action not reported.

**Duration:** of action *IV:* 15-90 minutes; half life reported to be 60 to 90 minutes.

**Availability:**

*Injection:*

0.4mg/mL 1 mL, Not PBS funded

0.4mg/mL 2 mL (pre-filled syringe), PBS general benefit [1](0)

0.4mg/mL 5 mL, (pre-filled syringe), PBS general benefit [1](0)

Currently the only PBS funded products are the Naloxone Min-I-Jets®.

**Notes:**

- most appropriately given IV, if not practical can be given IM or SC.
- reversal of respiratory depression will result in reversal of analgesia and withdrawal symptoms if physiologically dependent.
- In renal failure, with methadone and with opioids possessing depot action (transdermal preparations of fentanyl or buprenorphine) there may be a need to continue naloxone for extended periods as narcosis may persist greater than 24 hours.

## NAPROXEN

Inza®, Naprosyn®, Naprosyn SR®, Proxen SR®, Anaprox®, Crysanal®

**Class:** Non-steroidal anti-inflammatory drug (NSAID).

**Licensed indications:** rheumatoid arthritis (including juvenile arthritis), osteoarthritis, ankylosing spondylitis, pain associated with inflammation.

**Recognised other use(s) in palliative care:** itch, sweating, dysfunctional uterine bleeding, gout, fever.

**Contraindications/cautions:** proven allergy to naproxen, gastro-intestinal ulceration, asthma (in NSAID sensitive patients), cardiac impairment.

### Specific considerations:

*Hepatic impairment:* doses should be reduced in hepatic impairment, use with caution in severe impairment; increased risk of bleeding.

*Renal impairment:* pre-existing renal impairment increases the risk of NSAID-induced renal impairment; increased risk of bleeding. Avoid use in moderate-to-severe renal impairment.

### Adverse reactions:

*Common:* gastro-intestinal ulceration (more common in the elderly), diarrhoea, indigestion, nausea.

*Less common:* dizziness, rash, nephrotoxicity, hepatitis, oedema, hypertension, headache, tinnitus, proctitis, may prolong bleeding time.

### Interactions:

Naproxen is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

Additive effects with other nephrotoxic drugs.

Naproxen may reduce the effect of diuretics and antihypertensives.

### Dosage:

Note: Naproxen sodium is used in some formulations, 500 mg naproxen is equivalent to 550mg naproxen sodium; doses below are expressed as naproxen:

*Oral (normal release):* 500-1000mg per day in two divided doses.

*Oral (sustained release):* 750-1000mg per day as a single dose.

Regimes differ slightly for various indications, maximum dose for any indication is 1250 mg daily.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** inhibits prostaglandin synthesis through the inhibition of cyclo-oxygenase which is present in both COX-1 and COX-2 forms. Inhibition of COX-1 is associated with impaired gastric cytoprotection and anti-platelet function. Inhibition of COX-2 is associated with anti-inflammatory and analgesic action. Reduction in Glomerular Filtration Rate and renal blood flow is associated with both COX-1 and COX-2 inhibition.

**Onset:** of action 20 to 30 minutes.

**Peak:** of action 2 to 4 hours after oral (normal release) dosing.

**Duration:** of action around 7 hours from single doses, may be longer with repeated dosing; half-life is around 12 to 15 hours.

### Availability:

\* Products contain naproxen sodium, 550 mg naproxen sodium = 500 mg naproxen

*Tablets (normal release, scored and unscored):*

250mg, PBS restricted benefit [100](3)<sup>1</sup>, Palliative Care authority [100](3)<sup>2</sup>[100](0)<sup>3</sup>

275mg\*, Not PBS funded

500mg, PBS restricted benefit [50](3)<sup>1</sup>, Palliative Care authority [50](3)<sup>2</sup>[100](0)<sup>3</sup>

550mg\*, PBS restricted benefit [50](3)<sup>1</sup>, Palliative Care authority [50](3)<sup>2</sup>[100](0)<sup>3</sup>

*Tablets (controlled release):*

750mg, PBS restricted benefit [28](3)<sup>1</sup>, Palliative Care authority [28](3)<sup>2</sup>[100](0)<sup>3</sup>

1000mg, PBS restricted benefit [28](3)<sup>1</sup>, Palliative Care authority [28](3)<sup>2</sup>[100](0)<sup>3</sup>

*Oral liquid:*

25mg/mL, 474 mL, PBS authority benefit [1](3)<sup>4</sup>

Naproxen preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**PBS notes:**

1. chronic arthropathies (including osteoarthritis) with an inflammatory component; bone pain due to malignant disease.
2. initial supply (for up to 4 months) for palliative care patients where severe pain is a problem; continuing supply for palliative care patients where severe pain is a problem, and where consultation with a palliative care specialist or service has occurred.
3. continuing supply for palliative care patients where severe pain a problem.
4. chronic arthropathies (including osteoarthritis) with an inflammatory component in patients unable to take a solid dose form of a non-steroidal anti-inflammatory agent; bone pain due to malignant disease in patients unable to take a solid dose form of a non-steroidal anti-inflammatory agent.

**Notes:**

- Unless contra-indicated, NSAIDs such as naproxen should be given alongside regular full-dose paracetamol to provide optimal effect.
- NSAIDs (with paracetamol as above) are an effective co-analgesic when given with opioids in the treatment of bone and soft tissue pain.
- gastric cytoprotection with a proton pump inhibitor e.g. omeprazole should be considered routinely for palliative care patients requiring systemic NSAIDs.

## **NIFEDIPINE**

*Adalat®*, *Adalat Oros®*, *Addos XR®*, *Adefin®*, *Adefin XL®*, *Nifehexal®*, *Nyefax®*

**Class:** Calcium channel blocker – dihydropyridine.

**Licensed indications:** hypertension, angina.

**Recognised other use(s) in palliative care:** hiccoughs.

**Contraindications/cautions:** proven allergy to nifedipine, cardiogenic shock, heart failure, hypotension.

**Specific considerations:**

*Hepatic impairment:* may require a dose reduction in hepatic impairment.

*Renal impairment:* not reported to require dose adjustment in renal impairment.

**Adverse reactions:**

*Common:* peripheral oedema, headache, fatigue, dizziness, flushing, nausea, abdominal pain.

*Less common:* pulmonary oedema, hypotension, tachycardia, chest pain, dyspepsia, gingival hyperplasia, constipation, paraesthesia, muscle cramps, polyuria, rash.

**Interactions:**

Nifedipine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low (especially at the low doses used in Palliative Care) and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other drugs that cause hypotension.

**Dosage:**

Hiccoughs: usually respond to low doses and can often be used prn.

*Oral (standard tablet):* 10mg prn, or 10mg tds, increased if necessary.

*Oral (CR tablet):* not usually used in palliative care.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** dihydropyridine calcium channel blocker, blocks the flow of calcium ions through the L-type calcium channels that is required for smooth muscle contraction, thus resulting in smooth muscle relaxation including vasodilation.

**Onset:** of action usually within 1 hour for standard tablets.

**Peak:** of action not reported; however peak plasma levels for *Adalat*: 1.5 to 4 hours.

**Duration:** of action for *Adalat*: around 12 hours, *Adalat Oros*: around 24 hours.

**Availability:**

*Tablets*

10mg, PBS general benefit [60](5)

20mg, PBS general benefit [60](5)

*Tablets (controlled release):*

20mg, PBS general benefit [60](5)

30mg, PBS general benefit [60](5)

60mg, PBS general benefit [60](5)

Nifedipine preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- Onset, peak and duration of effect will vary according to the formulation used

## **NITRAZEPAM**

Alodorm®, Mogadon®

**Class:** Benzodiazepine - hypnotic, anticonvulsant.

**Licensed indications:** sleep disorders.

**Recognised other use(s) in palliative care:** infantile spasms refractory to other treatments; myoclonic epilepsy refractory to other treatments; muscle spasm; nausea and vomiting (anxiety related).

**Contraindications/cautions:** proven allergy to nitrazepam, avoid sudden withdrawal, respiratory depression, sleep apnoea, myasthenia gravis.

### **Specific considerations:**

*Hepatic impairment:* contraindicated in severe hepatic impairment, especially when hepatic encephalopathy is present. In mild-to-moderate impairment, use low doses of a short acting benzodiazepine to reduce risk of precipitating coma.

*Renal impairment:* increased sensitivity to CNS effects; use a lower initial dose in severe renal impairment.

### **Adverse reactions:**

*Common:* sedation, dizziness.

*Less common:* respiratory depression (high dose), disorientation, depression, disinhibition, amnesia.

### **Interactions:**

Nitrazepam is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. Although there are few reports of interactions specifically affecting nitrazepam, some of the interactions known to affect other benzodiazepines e.g. diazepam or midazolam may apply to nitrazepam. However, in the absence of data specific to nitrazepam, concerns about interactions should not deter efforts to optimise symptom control where appropriate.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

### **Dosage:**

*Oral:* for sleep 5-20mg at night; for epilepsy titrate to effect.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** may enhance the effect of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.

**Onset:** of action within 20 to 30 minutes.

**Peak:** of action not reported; however plasma levels peak within around 2 hours.

**Duration:** of action around 6 to 10 hours; half life ranges from 10 to 40 hours.

### **Availability:**

*Tablets (scored):*

5mg, PBS general benefit [25](0), PBS Authority benefit [50](5)<sup>1</sup>, Palliative care authority [50](3)<sup>2</sup> [50](0)<sup>3</sup>

Nitrazepam preparations are available from a range of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. myoclonic epilepsy; malignant neoplasia (late stage); for use by patients who are receiving long-term nursing care on account of age, infirmity or other condition in hospitals, nursing homes or residential facilities and who have been demonstrated, within the past 6 months, to be benzodiazepine dependent by an unsuccessful attempt at gradual withdrawal; for use by a patient who is receiving long-term nursing care and in respect of whom a Carer Allowance is payable as a disabled adult and who has been demonstrated, within the past 6 months, to be benzodiazepine dependent by an unsuccessful attempt at gradual withdrawal.
2. initial supply (up to 4 months) for palliative care patients where insomnia is a problem; continuing supply for palliative care patients where insomnia is a problem, and where consultation with a palliative care specialist or service has occurred.
3. continuing supply for palliative care patients where insomnia is a problem.

**Notes:**

- See below for comparison with other benzodiazepines and zopiclone.

<b>Pharmacological properties and dose equivalents* for benzodiazepines and zopiclone</b>					
Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## **NORTRIPTYLINE**

Allegron®

**Class:** Antidepressant – tricyclic (TCA).

**Licensed indications:** major depression.

**Recognised other use(s) in palliative care:** neuropathic pain, nocturnal enuresis, urinary urge incontinence.

**Contraindications/cautions:** proven allergy to nortriptyline or amitriptyline, arrhythmias, recent myocardial infarction, epilepsy, urinary retention, closed angle glaucoma.

**Specific considerations:**

*Hepatic impairment:* halve the dose in severe hepatic impairment, consider measuring serum concentrations.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

*Common:* anticholinergic effects including dry mouth, blurred vision, urinary retention, drowsiness (tolerance may develop).

*Less common:* sweating, constipation, confusion, arrhythmias, tachycardia, postural hypotension.

**Interactions:**

Nortriptyline is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of nortriptyline may be increased by cytochrome inhibitors: e.g. cimetidine, fluoxetine, haloperidol, methylphenidate.

Concentration and effect of nortriptyline may be decreased by cytochrome inducers: e.g. carbamazepine, phenobarbitone, rifampicin.

Use in combination with methylphenidate may cause hypertension.

Additive effects with other cardiotoxic drugs.

Additive effects with other CNS depressant drugs.

Additive effects with other drugs that lower seizure threshold.

Additive effects with other serotonergic drugs, increasing risk of serotonin syndrome.

**Dosage:**

Depression:

*Oral:* 25-150mg at night (max of 50mg in elderly).

Pain:

*Oral:* 10-50mg at night.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** TCAs inhibit reuptake of noradrenaline and serotonin into pre-synaptic terminals. They also block cholinergic, histaminergic and  $\alpha_1$ -adrenergic receptors. The action of TCAs in pain is unclear but may be related to effects on serotonin and noradrenaline in the descending pain pathways.

**Onset:** of action around 2-6 weeks in depression, several days in pain.

**Peak:** of action not reported.

**Duration:** of action around 24 hours; half-life reported to be in range 15 to 39 hours.

**Availability:**

*Tablets:*

10mg, PBS restricted benefit [50](2)<sup>1</sup>

25mg, PBS restricted benefit [50](2)<sup>1</sup>

Nortriptyline preparations currently only available as the brand Allegron®.

PBS notes:

1. major depression where other antidepressant therapy has failed; major depression where other antidepressant therapy is contraindicated.

**Note:**

- nortriptyline is the main metabolite of amitriptyline and tends to produce less adverse effects than amitriptyline.

## **NYSTATIN**

*Mycostatin®*, *Nilstat®*

**Class:** Antifungal – polyene.

**Licensed indications:** fungal infections: topical, oral, gastro-intestinal, vaginal.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to nystatin.

**Specific considerations:**

*Hepatic impairment:* not applicable as not absorbed or used systemically.

*Renal impairment:* not applicable as not absorbed or used systemically.

**Adverse reactions:**

Adverse reactions to topical treatment uncommon.

*Less common:* nausea, vomiting, diarrhoea (at high doses), local irritation.

**Interactions:**

None known.

**Dosage:**

Superficial fungal infection of skin:

*Topical:* apply two to three times a day.

Vaginal candidiasis:

*Vaginal:* 1 applicatorful of cream vaginally at night for 14 days.

Gastrointestinal candidiasis:

*Oral:* 500,000 units four times a day.

Oral candidiasis:

*Oral:* 100,000 units four times a day.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** increases fungal cell membrane permeability through binding to ergosterol in fungal cell membranes to allow leakage of intracellular particles.

**Onset:** of action not reported.

**Peak:** of action not reported.

**Duration:** of action not reported.

**Availability:**

*Tablets:*

500,000 units, PBS general benefit [50](0)

*Capsules:*

500,000 units, PBS general benefit [50](0)

*Oral liquid:*

100,000 units/mL 24 mL, PBS general benefit [1](1)

*Cream (vaginal):*

100,000 units/dose, 75g, RPBS benefit

*Cream:*

100,000 units/g, 15 g, PBS authority benefit [2](3)<sup>1</sup>, RPBS [1](1)

Some Nystatin preparations are available from a range of manufacturers and may contain a variety of excipients; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

I. PBS authority for fungal or yeast infection in an Aboriginal or Torres Strait Islander person.

**Notes:**

- if fungal infection is severe or recurrent use a systemic antifungal such as fluconazole or ketoconazole.

# OCTREOTIDE

Sandostatin®, Sandostatin LAR®

**Class:** Growth hormone inhibitor.

**Licensed indications:** acromegaly where surgery or radiotherapy are contraindicated or have failed to control disease; post pancreatic surgery; relief of symptoms associated with gastroenteropancreatic endocrine tumours (e.g. carcinoid tumours, VIPomas).

**Recognised other use(s) in palliative care:** antisecretory in intestinal obstruction, secretory diarrhoea, high fistula output, pain.

**Contraindications/cautions:** proven allergy to octreotide; insulinoma: possible increase in severity and duration of hypoglycaemia; diabetes: variable effect on blood glucose, adjust dose of insulin and oral antidiabetic drugs; gastroenteropancreatic endocrine tumours: occasional sudden escape from symptomatic control with rapid recurrence of severe symptoms.

**Specific considerations:**

*Hepatic impairment:* half-life may be increased in cirrhosis, requiring an adjustment of the maintenance dose.

*Renal impairment:* no dose adjustment of octreotide dosing is necessary.

**Adverse reactions:**

*Common:* abdominal pain, flatulence, nausea, vomiting, diarrhoea, gallstones, fatigue, hyperglycaemia, hypoglycaemia, hair loss, transient injection site reaction, bradycardia (rare in conditions other than acromegaly).

*Less common:* hypothyroidism, pancreatitis, hepatic dysfunction.

**Interactions:**

Octreotide is an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Octreotide may inhibit the metabolism and increase the concentration and effect of: carbamazepine and warfarin.

**Dosage:**

Variable depending on indication, in palliative care typically:

*SC (standard formulation only):* 0.2-0.6mg/24 hours (maximum 1mg/24 hours).

**Syringe driver:** see syringe driver compatibility table.

**Mechanism of action:** inhibits the release of growth hormone and various peptides of the gastroenteropancreatic endocrine system, has a more prolonged action than somatostatin (the natural growth hormone inhibiting peptide).

**Onset:** of action 20 to 40 minutes.

**Peak:** of action 20 to 40 minutes.

**Duration:** of action 8 to 12 hours.

**Availability:**

*Injection:*

0.05mg/mL 1 mL, PBS Section 100 availability only

0.1mg/mL 1 mL, PBS Section 100 availability only

0.5mg/mL 1 mL, PBS Section 100 availability only

*Long acting injection (powder and solvent):*

10mg, PBS Section 100 availability only

20mg, PBS Section 100 availability only

30mg, PBS Section 100 availability only

Some octreotide preparations are available from a range of manufacturers and may contain a variety of excipients; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- store at 2-8°C and protect from light
- the place of the long acting octreotide formulation Sandostatin LAR® in Palliative Care practice has not yet been established.

## OLANZAPINE

Zyprexa®

**Class:** Antipsychotic – atypical.

**Licensed indications:** schizophrenia and related psychoses, acute mania, maintenance treatment in bipolar disorder.

**Recognised other use(s) in palliative care:** delirium, pain, mood modification.

**Contraindications/cautions:** proven allergy to olanzapine, Parkinson's disease, epilepsy, hyperthyroidism, arrhythmia, glaucoma, prostatism, urinary retention.

**Specific considerations:**

*Hepatic impairment:* use with caution in hepatic impairment, consider dose reduction.

*Renal impairment:* use with caution in renal impairment, consider dose reduction.

**Adverse effects:**

Note: the extra pyramidal adverse effects usually associated with older (typical) antipsychotics appear to be less common with olanzapine.

*Common:* hyperglycaemia, weight gain, type 2 diabetes, peripheral oedema, constipation, orthostatic hypotension.

*Infrequent:* extra pyramidal side effects, akathisia, elevation of liver transaminases,

*Rare:* rhabdomyolysis, neuroleptic malignant syndrome, SIADH, Stevens-Johnson syndrome.

**Interactions:**

Olanzapine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that affect this system:

Concentration and effect of olanzapine may be decreased by cytochrome inducers: e.g. carbamazepine and tobacco smoke.

Additive effects with other CNS depressant drugs.

Additive effects with other anticholinergic drugs.

Additive effects with other drugs that prolong the QT interval, increasing risk of arrhythmias.

**Dosage:**

Delirium: (Note: 2<sup>nd</sup> line treatment, sedating, for mild to moderate symptoms, by oral or buccal route only):

*Oral / buccal:* 2.5-5mg twice a day regularly, plus additional as required doses of 2.5mg, total dose required usually 5-20mg/24 hours.

Pain (adjunct):

*Oral / buccal:* initial dosage 2.5–5mg daily, titrated to effect, maximum 20mg daily.

**Syringe driver:** not applicable.

**Mechanism of action:** in common with other antipsychotics, olanzapine is a dopamine antagonist; specifically it is a potent antagonist of D<sub>1</sub>, D<sub>2</sub>, D<sub>4</sub> receptors, with additional effects as a serotonin (5HT<sub>2A</sub>, 5HT<sub>2C</sub>) receptor antagonist.

**Onset:** of action hours to days in delirium; days to weeks in psychoses.

**Peak:** of action not reported; however peak plasma levels *Oral:* 5 to 8 hours; *IM:* 15 to 45 minutes.

**Duration:** of action ranges from 12 to 48 hours.

**Availability:**

*Tablets:*

2.5mg, PBS authority benefit [28](5)<sup>1</sup>

5mg, PBS authority benefit [28](5)<sup>1</sup>

7.5mg, PBS authority benefit [28](5)<sup>1</sup>

10mg, PBS authority benefit [28](5)<sup>1</sup>

*Wafers:*

5mg, PBS authority benefit [28](5)<sup>1</sup>

10mg, PBS authority benefit [28](5)<sup>1</sup>

*Injection:*

10mg (powder), Not PBS funded

Olanzapine preparations currently only available as the brand Zyprexa®.

PBS notes:

1. PBS authority for schizophrenia; maintenance treatment of bipolar disorder.

**Notes:**

- use the lowest effective dose, extrapyramidal reactions and hypotension are relatively uncommon at the lower end of the dose range.
- anticholinergic effects may be significant, especially at doses > 10mg/24 hours.
- avoid using conventional (“typical”) antipsychotics (e.g. haloperidol, chlorpromazine etc) for short term management of anxiety, agitation or disturbed behaviour outside the hospital setting, benzodiazepines may be more appropriate.

## OMEPRAZOLE

Losec® , Acimax® , Omepral® , Meprazole® , Probitor®

**Class:** Proton pump inhibitor (PPI) - ulcer healing/prophylactic.

**Licensed indications:** peptic ulcer disease; gastro-oesophageal disease; Zollinger –Ellison syndrome; H. Pylori eradication as part of combined treatment; treatment and prevention of peptic ulceration and erosion associated with NSAIDs.

**Recognised other use(s) in palliative care:** scleroderma oesophagus.

**Contraindications/cautions:** proven allergy to omeprazole or esomeprazole.

### Specific considerations:

*Hepatic impairment:* risk of accumulation when higher doses are used in hepatic impairment, monitor for adverse effects, some authorities recommend limiting the dose to 20mg per day.

*Renal impairment:* dose adjustment is not required in patients with impaired renal function.

### Adverse reactions:

*Common:* headache, nausea, vomiting, diarrhoea, constipation.

*Less common:* insomnia, dizziness, vertigo, pruritus, blood disorders, muscle pain, joint pain, dry mouth, agitation.

*Rare:* alopecia, confusion, haemolytic anaemia.

### Interactions:

Omeprazole is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate (see below for effect omeprazole may have on other drugs).

Omeprazole is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs and where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Omeprazole may inhibit the metabolism and increase the concentration and effect of: diazepam, phenytoin and warfarin.

Omeprazole may decrease the absorption of ketoconazole.

### Dosage:

*Oral:* 10-40mg once a day.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** inhibits gastric acid secretion via proton pump blockade, suppressing both stimulated and basal acid secretion.

**Onset:** of action typically within 30 minutes.

**Peak:** of action not reported; however plasma levels peak within 3 to 6 hours.

**Duration:** of action up to 24 hours; half-life reported as 0.5 to 3 hours.

### Availability:

*Tablets (enteric coated):*

10mg, PBS restricted benefit [30](5)<sup>1</sup>

20mg, PBS restricted benefit [30](5)<sup>1</sup>[30](1)<sup>2</sup>

*Capsules (enteric coated):*

20mg, PBS restricted benefit [30](5)<sup>1</sup> [30](1)<sup>2</sup>

Omeprazole preparations are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. gastro-oesophageal reflux disease; scleroderma oesophagus; Zollinger-Ellison syndrome.
2. initial treatment of peptic ulcer.

**Notes:**

- Proton Pump Inhibitors are considered the drugs of choice for prophylaxis or treatment of NSAID-induced GI damage.

# ONDANSETRON

Zofran®, Zofran Zydis®, Ondaz®, Ondaz Zydis®, Onsetron®

**Class:** Antiemetic – 5HT<sub>3</sub> antagonist.

**Licensed indications:** nausea and vomiting post-chemotherapy, post-radiotherapy, post-operatively.

**Recognised other use(s) in palliative care:** nausea and vomiting due to other causes, administration by subcutaneous injection for any clinical indication.

**Contraindications/cautions:** proven allergy to ondansetron, risk factors for prolonged QT interval.

**Specific considerations:**

*Hepatic impairment:* consider reducing dose in moderate to severe impairment, some sources recommend limiting dose to 8mg per day.

*Renal impairment:* no alteration of daily dosage or frequency of dosing is required.

**Adverse reactions:**

*Common:* headache, constipation.

*Less common:* hiccoughs, injection site reaction, dizziness, cardiac effects (usually with IV, including tachycardia, chest pain, arrhythmias), sedation, convulsions.

**Interactions:**

Ondansetron is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of ondansetron may be decreased by some cytochrome inducers: e.g. phenytoin and rifampicin.

Additive effects with other drugs that prolong the QT interval, increasing risk of arrhythmias.

Combination of IV ondansetron and IV metoclopramide has been associated with increased risk of cardiac arrhythmias.

Ondansetron may reduce analgesic effect of tramadol.

**Dosage:**

*Oral (including wafers):* 4-8mg twice a day.

*SC:* not usually used.

*Rectal:* not usually used.

**Syringe driver:** not usually give SC, therefore not applicable.

**Mechanism of action:** acts on 5HT<sub>3</sub> receptors in the vomiting centre in the central nervous system and in the gut.

**Onset:** of action *Oral:* within 30 minutes; *IV:* within 5 minutes.

**Peak:** of action *Oral:* 1 to 2 hours, *Rectal:* 6 hours.

**Duration:** of action around 12 hours; half-life around 3 to 5 hours.

**Availability:**

*Tablets:*

4mg, PBS restricted benefit [4](0)<sup>1</sup>, PBS authority benefit 10](1)<sup>2</sup>

8mg, PBS restricted benefit [4](0)<sup>1</sup>, PBS authority benefit 10](1)<sup>2</sup>

*Wafer:*

4mg, PBS restricted benefit [4](0)<sup>1</sup>, PBS authority benefit 10](1)<sup>2</sup>

8mg, PBS restricted benefit [4](0)<sup>1</sup>, PBS authority benefit 10](1)<sup>2</sup>

*Oral liquid:*

0.8mg/mL, PBS authority benefit [50mL](1)<sup>2</sup>

*Suppositories:*

16mg, Not PBS funded

*Injection:*

2mg/mL 2mL, PBS restricted benefit [4](0)<sup>1</sup>, PBS authority benefit [1](0)<sup>2</sup>

2mg/mL 4mL, PBS restricted benefit [4](0)<sup>1</sup>

Ondansetron preparations are available from a range of manufacturers and may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**PBS Notes:**

1. management of nausea and vomiting associated with cytotoxic chemotherapy being used to treat malignancy.
2. management of nausea and vomiting associated with radiotherapy being used to treat malignancy.

**Notes:**

- use in palliative care is outside the product license.
- may be of use in nausea and vomiting refractory to other antiemetics, particularly in gut malignancy where there is a greater release of 5HT.

## OXYBUTYNIN

Ditropan®, Oxytrol®

**Class:** Anticholinergic.

**Licensed indications:** urinary frequency, urgency or incontinence

**Recognised other use(s) in palliative care:** bladder spasm, spasm associated with urological catheter.

**Contraindications/cautions:** proven allergy to oxybutynin, gastro-intestinal obstruction or atony, urinary obstruction, myasthenia gravis, cardiac arrhythmias, coronary heart disease, heart failure, prostatic hypertrophy, inflammatory bowel disease, gastro-oesophageal reflux, fever, high ambient temperature, closed angle glaucoma, elderly, children.

**Specific considerations:**

*Hepatic impairment:* should be used with caution.

*Renal impairment:* should be used with caution.

**Adverse reactions:**

*Common:* dry mouth, constipation, urinary retention, blurred vision, mydriasis, application site reactions (for patch), nausea, vomiting, dyspepsia, dry eyes, tachycardia, arrhythmia, dizziness, drowsiness, headache, memory impairment, insomnia, worsening of dyskinesia, generalised choreic movements, fever due to anhydrosis, rash, facial flushing (more common in children).

*Less common:* confusion, hallucinations, anxiety, paranoia.

**Interactions:**

Oxybutynin is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, with the possible exception of ketoconazole which may increase the concentration and effect of oxybutynin; the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Cholinergic drugs antagonise effect of oxybutynin.

Additive effects with other anticholinergic drugs, with the risk of central anticholinergic delirium.

**Dosage:**

*Oral:* usually 2.5–5mg 2–3 times daily; maximum 20mg daily in 2 to 3 divided doses.

In the elderly, start with 2.5mg at night and increase slowly if necessary.

*Patch:* 1 patch applied twice a week (every 3–4 days).

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** blocks muscarinic actions of acetylcholine, in the urological tract this produces a reduction in bladder muscle contractility and increases bladder capacity.

**Onset:** of action *Oral:* 30 to 60 minutes.

**Peak:** of action not reported; however peak plasma levels *Oral:* 30 to 60 minutes; *Patch:* between 24 and 48 hours.

**Duration:** of action 6 to 10 hours; half-life around 2 hours.

**Availability:**

*Tablets (scored):*

5mg, PBS restricted benefit [100](5)<sup>1</sup>

*Transdermal Patch:*

3.9mg/24 hours, Not PBS funded

Oxybutynin tablets are available from a range of manufacturers and may contain a variety of excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. restricted benefit: detrusor overactivity.

**Notes:**

Additional information relevant to the patch formulation of oxybutynin:

- should be applied to dry, unbroken skin on abdomen, hip or buttock.
- should be removed after 3 to 4 days and replaced with a new patch applied to a different area.
- do not apply a patch to the same area within 7 days.
- patches may be associated with a lower incidence of dry mouth than tablets.
- skin reactions at the patch application site are common (> 1 in 10) and may be intolerable for some patients.

## OXYCODONE

Endone®, Oxynorm®, Oxycontin®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid.

**Licensed indications:** severe pain (more effective in nociceptive than in neuropathic/visceral pain).

**Recognised other use(s) in palliative care:** dyspnoea, cough, diarrhoea.

**Contraindications/cautions:** proven allergy to oxycodone.

Note: past nausea or hallucinations with opioids are not contraindications.

**Specific considerations:**

*Hepatic impairment:* in end-stage liver disease, doses should be reduced and the dosing interval increased.

*Renal impairment:* reduce dose if creatinine clearance <30 mL/minute.

**Adverse reactions:**

All opioids share a common range of adverse effects, although these are dose dependent and affected by circumstances of use. There is however significant variation between individuals in their response to different opioids and the different opioids have metabolites which may add to the adverse effects. Switching (rotating) to another, chemically distinct, opioid may therefore be useful to reduce adverse effects by allowing a wash out of these metabolites and presenting the mu receptors with a "fresh" opioid configuration.

**Common:** Constipation occurs in up to 90% of patients on opioids, always ensure there is a bowel control plan with laxatives. Although oxycodone may be less constipating than morphine, this increases with continued use. Nausea and vomiting are usually transient in the first few (1-5) days and may require metoclopramide or haloperidol to prevent symptoms. Transient confusion and sedation are also common, if persistent they will necessitate a reduction in the opioid dose or switching to another opioid. Dry mouth, dizziness and visual difficulty (particularly problems with accommodation) are also common.

**Less Common:** respiratory depression (usually only at high doses but does occur in the opioid naive when there is no titration of dosage, naloxone can reverse respiratory depression but will also reverse analgesia), myoclonic jerking, delirium, pruritus.

Respiratory depression is a serious side effect of opioids but is a symptom which is uncommon in Palliative Medicine where titration of opioids to pain or breathlessness is the norm. Respiratory rate reduction is often a late manifestation of opioid toxicity, but sedation is a better indicator and can be monitored by using a sedation score such as:

Sedation Score	
Score	Sedation level
0	wide awake
1	easy to rouse
2	easy to rouse, but cannot stay awake
3	difficult to rouse

With opioids, the aim is to keep sedation to a level of less than 2 on this scale.

Adverse effects, including respiratory depression, will persist for longer if there has been accumulation of oxycodone (e.g. due to hepatic or renal impairment) or where modified-release preparations have been used; extended monitoring may therefore be required.

Rare: visual hallucinations, hyperalgesia, biliary/urinary tract spasm, physical dependence (irrelevant in palliative care), SIADH, anaphylaxis, seizure,

#### **Interactions:**

Oxycodone is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of oxycodone may be increased by some cytochrome inhibitors: e.g. fluconazole, ketoconazole.

Concentration and effect of oxycodone may be decreased by some cytochrome inducers: e.g. rifampicin.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

#### **Dosage:**

Pain: dosage depends on whether the patient is opioid naive or already on opioids.

Opioid naive: **It is not recommended to start opioid naive patients on a controlled release oxycodone preparation, such patients should be titrated to effect with normal release tablets or liquid initially.**

*Oral*: initially 2.5–5mg (normal release) every 4-6 hours, titrated to effect (older patients require lower doses).

*SC*: initially 1.25-2.5mg every 4-6 hours, titrated to effect (older patients require lower doses)

Already on opioid: **Initial dose should be dependent on previous opioid exposure, it is recommended to start with an equianalgesic dose of oxycodone normal release tablets or liquid and titrate to effect.**

Once stable dosage has been achieved, switching to the controlled release preparation can be achieved by giving half the total 24 hour dose every 12 hours.

Rescue doses of 1/12th or 1/6th of the total 24 hour dose should always be prescribed so as to be available to manage occasional breakthrough pain.

**Syringe driver:** see syringe driver compatibility chart.

**Mode of action:** stimulates mu (and other) opioid receptors in the descending inhibitory pathways of the CNS and in the GIT. Cough suppression occurs through effects in the medullary centre of the brain.

**Onset:** of action *Oral (standard tablets)*: 10 to 30 minutes; *Oral (CR tablets)*: 1 hour.

**Peak:** of action not reported; however peak plasma levels *Oral (standard tablets)*: 1 to 1.5 hours; *Oral (CR tablets)*: 3 hours.

**Duration:** of action *Oral (standard tablets)*: 3 to 6 hours; *Oral (CR tablets)*: 12 hours.

#### **Availability:**

*Tablets (scored):*

5mg, PBS restricted benefit [20](0) <sup>1</sup>

*Tablets (controlled release):*

5mg, PBS restricted benefit [20](0) <sup>2</sup>

10mg, PBS restricted benefit [20](0) <sup>2</sup>

20mg, PBS restricted benefit [20](0) <sup>2</sup>

40mg, PBS restricted benefit [20](0) <sup>2</sup>

80mg, PBS restricted benefit [20](0) <sup>2</sup>

*Capsules:*

5mg, PBS restricted benefit [20](0)<sup>1</sup>

10mg, PBS restricted benefit [20](0)<sup>1</sup>

20mg, PBS restricted benefit [20](0)<sup>1</sup>

*Oral liquid:*

1mg/mL 250 mL, PBS restricted benefit [1](0)<sup>1</sup>

*Suppositories:*

30mg, PBS restricted benefit [12](0)<sup>1</sup>

*Injection:*

10mg/mL 1 mL & 2 mL, not PBS funded, available through Special Access Scheme

Different oxycodone preparations may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**PBS notes:**

1. severe disabling pain not responding to non-narcotic analgesics.
2. chronic severe disabling pain not responding to non-narcotic analgesics.

**Notes:**

- oxycodone may be tried as an alternative opioid for patients intolerant of morphine.
- do not use controlled release tablets for acute or breakthrough pain.
- suppositories may have variable absorption, but typically have a slower onset of action and longer effect than standard oral formulations of oxycodone.
- a small percentage of patients with Caucasian heritage may lack the gene necessary to metabolise oxycodone.

## **PAMIDRONATE DISODIUM**

Aredia®, Pamisol®

**Class:** Bisphosphonate.

**Licensed indications:** hypercalcaemia, metastatic bone pain, Paget's disease.

**Recognised other use(s) in palliative care:** prevention and treatment of osteoporosis (including postmenopausal and corticosteroid-induced).

**Contraindications/cautions:** proven allergy to pamidronate, multiple myeloma, hypocalcaemia.

### **Specific considerations:**

*Hepatic impairment:* in mild to moderate hepatic impairment, manufacturer suggests reducing infusion rate to <20mg/hour, no data in severe impairment.

*Renal impairment:* if creatinine clearance <30 mL/minute, avoid use unless life-threatening hypercalcaemia is present. In less severe renal impairment reduce infusion rate to <20mg/hour. Due to the risk of acute renal failure, monitor renal function if there is a predisposition to renal impairment.

### **Adverse reactions:**

*Less common:* transient flu-like symptoms, slight increase in temperature, fever, hypocalcaemia, transient bone pain, nausea, headache.

*Rare:* osteonecrosis of the jaw (more commonly associated with dental surgery).

### **Interactions:**

Additive effects with other nephrotoxic drugs.

Loop diuretics may cause increased electrolyte disturbance.

### **Dosage:**

Rate of infusion should not exceed 1mg/minute and concentration should not exceed 60mg/250mL.

Bone pain:

*IV Infusion:* 90mg every 3-4 weeks.

Hypercalcaemia:

*IV Infusion:* 15-90mg depending on serum calcium.

**Syringe driver:** not applicable.

**Mechanism of action:** decreases bone resorption by inhibiting osteoclasts.

**Onset:** of action in hypercalcaemia 1 to 2 days, in bone pain varies from hours to 1 week.

**Peak:** of action in hypercalcaemia: 4-5 days.

**Duration:** of action in hypercalcaemia 2 weeks to 3 months, bone pain 3 to 4 weeks.

### **Availability:**

*Injection (powder & solvent):*

15mg, PBS Authority<sup>1</sup> and Section 100<sup>2</sup>

30mg, PBS Authority<sup>1</sup> and Section 100<sup>2</sup>

90mg, PBS Authority<sup>1</sup> and Section 100<sup>2</sup>

*Injection:*

3mg/mL 5mL and 10mL, PBS authority benefit<sup>1</sup> and Section 100<sup>2</sup>

6mg/mL 10mL, PBS authority benefit<sup>1</sup> and Section 100<sup>2</sup>

9mg/mL 10mL, PBS authority benefit<sup>1</sup> and Section 100<sup>2</sup>

PBS notes:

1. PBS authority benefit for symptomatic Paget's disease of bone.
2. Section 100 for hypercalcaemia of malignancy, refractory to antineoplastic therapy; and; multiple myeloma; bone metastases from breast cancer.

**Notes:**

- 50% of patients with metastatic bone pain may be responsive.

# PANTOPRAZOLE

Somac®

**Class:** Proton pump inhibitor (PPI) - ulcer healing/prophylactic.

**Licensed indications:** peptic ulcer disease; GORD; Zollinger–Ellison syndrome; *H. pylori* eradication as part of an effective regimen; prevention of dyspepsia, peptic ulcer and erosions associated with NSAIDs in people at increased risk who need continuous nonselective NSAID treatment.

**Recognised other use(s) in palliative care:** scleroderma oesophagus.

**Contraindications/cautions:** proven allergy to pantoprazole.

**Specific considerations:**

*Hepatic impairment:* risk of accumulation when higher doses are used in hepatic impairment; monitor for adverse effects, consider increasing dosing interval to alternate days.

*Renal impairment:* limit daily dose to 40mg.

**Adverse reactions:**

*Common:* headache, nausea, vomiting, constipation.

*Less common:* abdominal pain, flatulence, insomnia, pruritus, dizziness, increased sweating.

*Rare:* myalgia, myopathy, nephritis.

**Interactions:**

Pantoprazole is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Pantoprazole (unlike omeprazole and esomeprazole) is reported to have no effect to induce or inhibit the Cytochrome P450 system.

Pantoprazole may decrease the absorption of ketoconazole.

**Dosage:**

*Oral:* 20-80mg once a day.

*Injection:* not usually used in palliative care.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** inhibits gastric acid secretion via proton pump blockade, suppressing both stimulated and basal acid secretion.

**Onset:** of action typically within 30 minutes.

**Peak:** of action not reported; however plasma levels peak around 2.5 hours after oral administration.

**Duration:** of action up to 24 hours; half-life is usually around 1 hour, increasing to 3 to 6 hours in those with cirrhosis.

**Availability:**

*Tablets (enteric coated):*

20mg, PBS restricted benefit [30](5)<sup>1</sup>

40mg, PBS restricted benefit [30](2)<sup>2</sup> [30](5)<sup>3</sup>

Currently only available as the brand Somac®

PBS notes:

1. Restricted benefit for gastro-oesophageal reflux disease.
2. Restricted benefit for initial treatment of peptic ulcer.

3. Restricted benefit for gastro-oesophageal reflux disease, scleroderma oesophagus, Zollinger-Ellison syndrome.

**Notes:**

- Proton Pump Inhibitors are considered the drugs of choice for prophylaxis or treatment of NSAID-induced gastro-intestinal damage.

## **PARACETAMOL (ACETAMINOPHEN)**

*Panadol®*, *Panamax®*, *Paralgin®*, *Chemadol®*, *Dymadon®*, *Febrido®*, *Parahexo®*, *Parmol®*, *Duatrol®*, *Panadol Osteo®*

(plus numerous over the counter medications and combination products)

**Class:** Analgesic – non-opioid.

**Licensed indications:** mild to moderate pain, fever.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to paracetamol, use of other paracetamol containing preparations including over the counter and combination products.

**Specific considerations:**

*Hepatic impairment:* patients with chronic liver disease may be at increased risk of liver damage following therapeutic doses or overdose of paracetamol, although hard evidence is lacking.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

Adverse reactions reported uncommonly.

*Less common:* rash, pancreatitis on prolonged use, liver damage in overdose (> 6g in 24 hours) or in combination with heavy alcohol intake, nephrotoxicity.

**Interactions:**

Hepatic enzyme inducers e.g. carbamazepine, phenobarbitone and phenytoin, may increase the risk of hepatotoxicity from paracetamol.

Domperidone or metoclopramide may increase absorption of paracetamol.

Paracetamol may occasionally increase the effect of warfarin.

**Dosage:**

*Oral (standard release):* 500mg-1g 4–6 hourly (maximum 4g daily).

*Oral (controlled release):* 1.33g 6–8 hourly swallowed whole (maximum 3.99g daily).

*Rectal:* 500mg-1g 4–6 hourly (maximum 4g daily).

*IV infusion:* 1g 4-6 hourly (maximum 4 g daily).

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** thought to have a central effect on pain pathways through the inhibition of prostaglandin synthesis centrally and to a lesser extent peripherally. The antipyretic effect may be due to its effect in the hypothalamus. Anti-inflammatory effects are clinically insignificant.

**Onset:** of action usually within 30 minutes of standard oral tablets.

**Peak:** of action not reported; however plasma levels peak 30 minutes to 2 hours after standard oral tablets.

**Duration:** of action around 4 to 6 hours; half-life ranges from 1 to 3 hours.

**Availability:**

*Tablets:*

500mg, PBS general benefit [100](1), PBS restricted benefit [300](4)<sup>1</sup>

*Tablets (controlled release):*

665mg, PBS restricted benefit [192](5)<sup>2</sup>, Palliative Care authority [192](3)<sup>3</sup> [192](0)<sup>4</sup>

*Oral liquid:*

24mg/mL, PBS general benefit [100mL](2)

48mg/mL, PBS general benefit [200mL](2)

*Suppositories:*

125mg, Not PBS funded

250mg, Not PBS funded

500mg, Palliative Care authority [24](3)<sup>3</sup> [24](0)<sup>4</sup>

*Injection:*

10mg/mL 50mL & 100mL, Not PBS funded

Paracetamol preparations are available from a range of manufacturers, different preparations may contain different excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. chronic arthropathies.
2. persistent pain associated with osteoarthritis.
3. initial supply (up to 4 months) for palliative care patients for analgesia or fever where alternative therapy cannot be tolerated; continuing supply for these patients where consultation with a palliative care specialist or service has occurred (3 repeats).
4. continuing supply for palliative care patients for analgesia or fever where alternative therapy cannot be tolerated (no repeats).

**Notes:**

- give paracetamol regularly rather than as required.
- unless contra-indicated, regular full-dose paracetamol should be given alongside an NSAID to provide optimal effect.
- paracetamol (with an NSAID as above) is an effective co-analgesic when given with opioids in the treatment of bone and soft tissue pain.
- fixed-dose paracetamol-opioid combination preparations not recommended.
- hepatic damage may occur in paracetamol overdose.

## **PHENOBARBITONE (PHENOBARBITAL)**

**Class:** Barbiturate – anticonvulsant.

**Licensed indications:** seizure control, status epilepticus.

**Recognised other use(s) in palliative care:** terminal restlessness.

**Contraindications/cautions:** proven allergy to phenobarbitone - consider possibility of cross-reactivity with other barbiturates, hypersensitivity syndromes with carbamazepine or phenytoin, acute intermittent porphyria, elderly.

**Specific considerations:**

*Hepatic impairment:* may need to reduce dose in hepatic impairment.

*Renal impairment:* may need to reduce dose in renal impairment.

**Adverse reactions:**

*Common:* drowsiness, headache.

*Less common:* gastro-intestinal upset, paradoxical excitement, pain, hypocalcaemia.

**Interactions:**

Phenobarbitone is metabolised by the Cytochrome P450 system and has a narrow therapeutic range, there is therefore a risk of clinically significant interactions when it is prescribed with some drugs that affect this system:

Concentration and effect of phenobarbitone may be increased by some cytochrome inhibitors: e.g. methylphenidate.

Concentration and effect of phenobarbitone may be decreased by some cytochrome inducers, although the literature contains few reports of clinically significant interactions.

Various interactions have been reported when phenobarbitone is given with other anticonvulsants that induce or inhibit the Cytochrome P450 system e.g. phenytoin, carbamazepine and valproate.

Phenobarbitone is also a potent inducer of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a high risk of clinically significant interactions:

Phenobarbitone may induce the metabolism and decrease the concentration and effect of: amitriptyline, buprenorphine, clonazepam, dexamethasone, fentanyl, flecainide, haloperidol, ketoconazole, methadone, metronidazole, nortriptyline, prednisolone, rifampicin and warfarin.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Additive effects with other hepatotoxic drugs, including paracetamol.

**Dosage:**

Terminal restlessness

SC: 600–1200mg/ 24 hours, be alert for irritation at injection site.

**Syringe driver:** Seek specialist advice. Phenobarbitone injection can cause significant irritation and it should therefore be diluted as much as possible to reduce reactions. In addition, it is incompatible with many other drugs and should be infused on its own to reduce the risk of such problems.

**Mechanism of action:** prolongs inhibitory postsynaptic potential by increasing the mean chloride channel opening time and prolongs the duration of gamma-aminobutyric acid (GABA) induced cell membrane hyperpolarisation.

**Onset:** of action not reported.

**Peak:** of action not reported; however peak plasma levels *Oral:* within 2 hours; *IM:* within 4 hours.

**Duration:** of action on chronic use exceeds 24 hours; half-life around 75 to 120 hours.

**Availability:**

*Tablets (scored):*

30mg, PBS restricted benefit [200](4)<sup>1</sup>

*Injection:*

200mg/mL 1 mL, PBS restricted benefit [5](0)<sup>1</sup>

Phenobarbitone tablets and injections currently only available from one manufacturer.

PBS notes:

1. restricted benefit for epilepsy.

**Notes:**

- risk of respiratory depression in overdose.
- very long half life.
- normal therapeutic range for phenobarbitone is 10-40 mg/L (45-180 micromol/L)

## PHENYTOIN

Dilantin®

**Class:** Anticonvulsant.

**Licensed indications:** epilepsy, including simple and complex partial seizures, generalised tonic-clonic seizures and status epilepticus.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to phenytoin, low albumin.

**Specific considerations:**

*Hepatic impairment:* may require dosage reduction in hepatic impairment.

*Renal impairment:* not reported to require dosage adjustment in renal impairment.

**Adverse reactions:**

*Common:* gingival hyperplasia, nausea, vomiting, insomnia, agitation, sedation, confusion, ataxia, skin reactions, coarse facies, hirsutism.

*Less common:* slurred speech, dizziness, blood disorders, hepatitis, Stevens-Johnson syndrome.

**Interactions:**

Phenytoin is metabolised by the Cytochrome P450 system and has a narrow therapeutic range, there is therefore a high risk of clinically significant interactions when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of phenytoin may be increased by some cytochrome inhibitors: e.g. cimetidine, esomeprazole, fluconazole, fluoxetine, ketoconazole, methylphenidate, metronidazole, miconazole, omeprazole.

Concentration and effect of phenytoin may be decreased by some cytochrome inducers: e.g. dexamethasone, rifampicin.

Phenytoin levels and effect may be increased or decreased by benzodiazepines.

Various interactions have been reported when phenytoin is given with other anticonvulsants that induce or inhibit the Cytochrome P450 system e.g. carbamazepine, phenobarbitone and valproate.

Additive effects with other CNS depressant drugs.

Phenytoin is also a potent inducer of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a high risk of clinically significant interactions:

Phenytoin may induce the metabolism and decrease the concentration and effect of: buprenorphine, clonazepam, dexamethasone, diazepam, fentanyl, flecainide, haloperidol, ketoconazole, methadone, mexiletine, midazolam, mirtazapine, ondansetron, prednisolone, rifampicin and warfarin.

Phenytoin may reduce the diuretic effect of frusemide.

Additive effects with other hepatotoxic drugs, including paracetamol.

**Dosage:**

*Oral:* 200-500mg/24 hours, in one or two divided doses.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** inhibits spread of seizure by preventing repetitive neuronal discharge through the motor cortex possibly via sodium channels.

**Onset:** of action not reported.

**Peak:** of action after 7 to 10 days, or after 8 to 12 hours if adequate loading dose given; plasma levels peak within 4 to 8 hours.

**Duration:** of action not reported; variable half-life with mean around 22 hours.

**Availability:**

*Tablets (phenytoin):*

50mg, PBS general benefit [200](2)

*Oral liquid (phenytoin):*

6mg/mL, PBS general benefit [500mL](3)

*Capsules (phenytoin sodium):*

30mg, PBS general benefit [200](2)

100mg, PBS general benefit [200](2)

*Injection (phenytoin sodium):*

50mg/mL 2 mL & 5 mL, Not PBS funded

Phenytoin preparations may be available from different manufacturers and contain different excipients e.g. colours, coatings etc; seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- monitor plasma concentrations.
- normal therapeutic range for phenytoin is 10–20 mg/L (40–80 micromol/L).
- measurement of free phenytoin (not bound to albumin) is recommended in patients with decreased albumin and chronic renal failure.
- small changes in dose may result in large changes in plasma concentration.
- 100 mg phenytoin sodium contains approximately 92 mg phenytoin.

## **POLYETHELENE GLYCOL LAXATIVES (e.g. MACROGOL 3350)**

*Movicol®*, *Movicol-Half®*

**Class:** Laxative – osmotic.

**Licensed indications:** constipation, faecal impaction.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to polyethylene glycols; partial or complete intestinal obstruction; bowel perforation; severe colitis; toxic megacolon.

**Specific considerations:**

*Hepatic impairment:* not significantly absorbed, no dose adjustment therefore required.

*Renal impairment:* not significantly absorbed, however use with caution in renal impairment as fluid and electrolyte disturbance may occur from effect.

**Adverse effects:**

*Common:* fluid and electrolyte disturbance, nausea, vomiting, diarrhoea, anal irritation, abdominal bloating, cramps and pain.

*Rare:* allergic reactions.

**Interactions:**

Additive toxicity may possibly occur as a result of fluid and electrolyte disturbance.

**Dosage:**

*Oral:* Movicol, 1 to 3 sachets daily to maximum of 8 sachets per day; or Movicol-Half, 1 to 6 sachets daily to a maximum of 16 sachets per day.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of Action:** polymer with osmotic laxative activity.

**Onset:** of action 1–2 days for constipation, 1–3 days for faecal impaction.

**Peak:** of action 1–2 days for constipation; 1–3 days for faecal impaction.

**Duration:** of action not applicable.

**Availability:**

*Powder for oral liquid:*

6.563g sachet: PBS restricted benefit [30](5)<sup>1</sup>

13.125g sachet: PBS restricted benefit [30](5)<sup>1</sup>, Palliative Care authority [30](5)<sup>2</sup> [30](0)<sup>3</sup>

Currently only available as the brands Movicol®, Movicol-Half®

PBS notes:

1. constipation in patients with malignant neoplasia; chronic constipation or faecal impaction not adequately controlled with first line interventions such as bulk-forming agents; paraplegic and quadriplegic patients and others with severe neurogenic impairment of bowel function not responding to other oral therapies.
2. initial supply (for up to 4 months) for palliative care patients where constipation is a problem; continuing supply for palliative care patients where constipation is a problem, and where consultation with a palliative care specialist or service has occurred.
3. continuing supply for palliative care patients where constipation a problem.

**Notes:** none.

## **PREDNISONE / PREDNISOLONE**

*Prednisone: Panafcort®*, *Predsone®*, *Sone®*

*Prednisolone: Panafcortelone®*, *Predsolone®*, *Solone®*, *Predmix®*, *Redipred®*

**Note: Prednisone is a pro-drug that is hepatically metabolised to active prednisolone. In severe hepatic impairment this conversion may be impaired and therefore the effect of prednisone may be less predictable than that of prednisolone.**

**Class:** Corticosteroid – glucocorticoid.

**Licensed indications:** allergy, asthma, rheumatic disease, inflammatory conditions.

**Recognised other use(s) in palliative care:** nausea, vomiting, inflammation in gastrointestinal obstruction, sweating, itch, hypercalcaemia, hiccough, pain, dyspnoea lymphangitis, liver capsule pain, tenesmus.

**Contraindications/cautions:** proven allergy to prednisone or prednisolone, infections, gastrointestinal bleeding, diabetes, congestive heart failure, mood disorders.

**Specific considerations:**

*Hepatic impairment:* caution is advised when using in hepatic impairment. In severe hepatic impairment the conversion of prednisone to prednisolone may be reduced.

*Renal impairment:* caution is advised when using in renal impairment.

**Adverse reactions:**

*Common:* insomnia (this can be decreased if given as a single dose in the morning).

*Less common:* sodium and fluid retention, gastro-intestinal ulceration, delayed wound healing, thinning of skin (on prolonged use), proximal muscle weakness, Cushing's syndrome, weight gain, depression, mania, delirium, increased glucose levels, may precipitate or unmask diabetes.

**Interactions:**

Prednisolone is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Prednisolone concentrations and effect may be increased by some cytochrome inhibitors: e.g. ketoconazole.

Prednisolone concentrations and effect may be decreased by some cytochrome inducers: e.g. carbamazepine, phenobarbitone, phenytoin and rifampicin.

Prednisolone may also induce the Cytochrome P450 system involved in the metabolism of other drugs. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate (see above for the effect other drugs may have on prednisolone).

Additive effects with other drugs that cause GI irritation, ulceration and bleeding.

**Dosage:**

*Oral:* 10-100 mg in 24 hours, given as a single dose in the morning where possible.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** decreases inflammatory response, thought to be via induction of the anti-inflammatory protein lipocortin.

**Onset:** of action variable, typically within 8 to 24 hours.

**Peak:** of action not reported; however plasma levels peak after 1 to 2 hours.

**Duration:** of action 12 to 36 hours; half life ranges from 2 to 4 hours.

**Availability:**

Prednisolone

*Tablets (scored):*

1mg, PBS general benefit [100](4)

5mg, PBS general benefit [60](4)

25mg, PBS general benefit [30](4)

*Oral liquid:*

5mg/mL, PBS general benefit [30mL](5)

Prednisone

*Tablets (scored):*

1mg, PBS general benefit [100](4)

5mg, PBS general benefit [60](4)

25mg, PBS general benefit [30](4)

Prednisone and prednisolone preparations are available from a range of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- 5mg prednisolone has an equivalent anti-inflammatory effect to 0.75mg dexamethasone or 20mg hydrocortisone.
- when discontinuing prednisone or prednisolone decrease the dose slowly (taper), unless the patient has been taking it for less than five days in which case dose tapering is not necessary.
- mood changes not usually seen with doses below 40mg prednisolone per day.
- corticosteroid-induced mood disorder is usually depression and rarely mania, paranoia and psychosis can occur.
- corticosteroid-induced insomnia may respond to hypnotics

# **PREGABALIN**

Lyrica®

**Class:** Antiepileptic – gamma-amino butyric acid (GABA) analogue.

**Licensed indications:** partial seizures, with or without secondary generalisation, not controlled satisfactorily by other antiepileptic drugs; neuropathic pain in adults.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to pregabalin, risk of aggravation of absence seizures.

## **Specific considerations:**

*Hepatic impairment:* no dosage adjustment required in hepatic impairment.

*Renal impairment:* reduce dose in renal impairment; daily doses should not exceed 300mg if creatinine clearance <60mL/min, 150mg if creatinine clearance <30mL/min and 75mg if creatinine clearance <15mL/min.

## **Adverse effects:**

*Common:* fatigue, sedation, dizziness, ataxia, tremor, diplopia, nystagmus, amblyopia, amnesia, abnormal thinking, hypertension, vasodilatation, peripheral oedema, dry mouth, weight increase, rash.

*Infrequent:* confusion, psychosis, hypoaesthesia, vertigo, myalgia, myoclonus, excessive salivation, heart failure.

*Rare:* neutropaenia, first degree heart block, pancreatitis, rhabdomyolysis, jaundice, movement disorders, allergic reactions.

## **Interactions:**

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

## **Dosage**

Partial seizures:

*Oral:* initially 75mg twice daily; if required, increase after 7 days to 150mg twice daily, to a maximum of 300mg twice daily.

Neuropathic pain:

*Oral:*, initially 75mg twice daily; if required, increase after 3 to 7 days to 150mg twice daily, to a maximum of 300mg twice daily.

**Syringe driver:** not given parenterally, therefore not applicable.

## **Mechanism of Action:**

Pregabalin is an analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) with analgesic, anxiolytic and anticonvulsant activity. It reduces calcium inflow at nerve terminals and decreases the release of several neurotransmitters including glutamate, noradrenaline and substance P.

**Onset:** of action in neuropathic pain around 24 hours, in epilepsy around 2 days.

**Peak:** of action not reported; however plasma levels peak within 1.5 hours.

**Duration:** of action around 12 hours; half-life is around 6 hours.

## **Availability:**

*Capsules:*

75mg, RPBS authority benefit

150mg, RPBS authority benefit

300mg, RPBS authority benefit

Currently only available as the brand Lyrica®.

PBS notes:

Repatriation PBS benefit only, for refractory neuropathic pain uncontrolled by other drugs.

**Notes:** none.

## **PROCHLORPERAZINE**

Stemetil®, Stemizine®

**Class:** Phenothiazine – antiemetic, antipsychotic, neuroleptic.

**Licensed indications:** nausea and vomiting, vertigo.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to prochlorperazine - consider possibility of cross-sensitivity with other phenothiazines, Parkinson's Disease.

**Specific considerations:**

*Hepatic impairment:* phenothiazines are hepatotoxic and may precipitate coma, avoid in moderate to severe hepatic impairment.

*Renal impairment:* start with small dose in severe renal impairment.

**Adverse reactions:**

*Common:* constipation, dry mouth, drowsiness, akathisia, parkinsonism, blurred vision, extra-pyramidal effects, hypotension, hyperprolactinaemia.

*Less common:* prolongation of QT interval.

**Interactions:**

Prochlorperazine is probably metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system.

However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Additive effects with other anticholinergic drugs.

Additive effects with other CNS depressant drugs.

Additive effects with other drugs that lower seizure threshold.

Additive effects with other drugs that prolong the QT interval, increasing the risk of arrhythmias.

**Dosage:**

Nausea and vomiting:

*Oral:* initially 20mg, then 10mg 2 hours later; if still required 5–10mg 3 times daily.

*IV/IM:* 12.5 mg every 8 hours as needed.

*Rectal:* 25mg followed by oral medication (if possible) 6 hours later.

Vertigo:

*Oral:* 5-10mg 2–3 times daily.

*IV/IM:* 12.5mg initially, then every 8 hours as needed.

**Syringe driver:** not for SC administration as highly irritant, may cause necrosis.

**Mechanism of action:** as an antiemetic has inhibitory effects on the chemoreceptor trigger zone; antipsychotic effects are manifested through blockade of dopamine (D<sub>2</sub>) receptors, also has anticholinergic, antihistaminergic, antiserotonergic and alpha-adrenergic blocking effects.

**Onset:** of action variable, typically 1 to 2 hours after oral dosing.

**Peak:** of action variable, typically 1 to 5 hours.

**Duration:** of action typically up to 8 hours; half life reported to be 6 to 7 hours.

**Availability:**

*Tablets:*

5mg, PBS general benefit [25](0)

*Suppositories:*

25mg, PBS general benefit [5](2)

*Injection:*

12.5mg/mL 1 mL, PBS general benefit [10](0)

Prochlorperazine tablets from different manufactures may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- although prochlorperazine is a phenothiazine and shares features of related drugs such as chlorpromazine, methotrimeprazine etc, its antipsychotic and sedative effects are more modest and its main clinical application is in nausea, vomiting and vertigo.
- rate of IV injection should not exceed 5mg/minute.

## PROMETHAZINE

Gold Cross Antihistamine Elixir®, Phenergan®, Phenergan Elixir®

**Class:** Phenothiazine – antihistamine, antiemetic.

**Licensed indications:** allergic conditions, e.g. rhinitis, conjunctivitis, urticaria, contact dermatitis; pruritus, nausea and vomiting (including motion sickness) sedation, premedication.

**Recognised other use(s) in palliative care:** administration by subcutaneous injection or infusion for any clinical indication (specialist use only).

**Contraindications/cautions:** proven allergy to promethazine - consider possibility of cross-sensitivity with other phenothiazines, epilepsy, respiratory depression.

**Specific considerations:**

*Hepatic impairment:* avoid, may precipitate coma in severe liver disease.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

*Common:* sedation, dizziness, tinnitus, blurred vision, euphoria, incoordination, anxiety, insomnia, tremor, nausea, vomiting, constipation, diarrhoea, epigastric discomfort, dry mouth, cough.

*Less common:* urinary retention, palpitations, hypotension, headache, hallucination, psychosis.

**Interactions:**

Additive effects with other CNS depressant drugs.

Additive effects with other anticholinergic drugs.

Additive effects with other drugs that lower seizure threshold.

Additive effects with other drugs that prolong the QT interval, increasing the risk of arrhythmias.

**Dosage:**

Promethazine is known to have potential for causing local irritation, it is therefore recommended that when used by routes other than oral, it should be given by deep IM injection and where IV administration cannot be avoided, it should be diluted and give at a rate not exceeding 25mg/minute. Most sources recommend that the SC route should be avoided due to the significant potential for irritation and tissue damage; however there is some specialist clinical experience with using this route in palliative care where other routes and other drugs cannot be used.

Nausea and vomiting:

*Oral:* 25mg every 4–6 hours as needed, maximum 100mg daily.

*SC:* see note above.

*IM/IV:* 12.5–25mg every 4–6 hours as needed.

Motion sickness:

*SC:* see note above.

*Oral* 25mg every 4–6 hours as needed, maximum 100 mg daily.

**Syringe driver:** see note above, seek specialist advice.

**Mechanism of action:** blocks histamine-1 receptors, has anticholinergic and anti-dopaminergic properties; may have direct action on the vestibular system.

**Onset:** of action *IM:* around 20 minutes; *IV:* 3 to 5 minutes.

**Peak:** of action *Oral:* 4.5 hours; *Rectal:* 6 to 9 hours.

**Duration:** of action around 2 to 6 hours; half-life 5 to 14 hours.

**Availability:***Tablets:*

10mg, Palliative Care authority [50](3)<sup>1</sup> [50](0)<sup>2</sup>, RPBS benefit [50](2)

25mg, Palliative Care authority [50](3)<sup>1</sup> [50](0)<sup>2</sup>, RPBS benefit [50](2)

*Oral liquid:*

1mg/mL, Palliative Care authority [100mL](3)<sup>1</sup> [100mL](0)<sup>2</sup>

*Injection:*

25mg/mL 2mL, PBS general benefit [10](0)

Currently each formulation is only available from one manufacturer.

**PBS notes:**

1. Initial supply (for up to 4 months) for palliative care patients where nausea and/or vomiting is a problem; continuing supply for palliative care patients where nausea and/or vomiting is a problem and where consultation with a palliative care specialist or service has occurred (3 repeats).
2. Continuing supply for palliative care patients where nausea and/or vomiting is a problem (no repeats).

**Notes:**

- rate of IV injection should not exceed 25mg/minute.

## **RANITIDINE**

*Ausran®*, *Rani 2®*, *Ranihexal®*, *Ranitic®*, *Ranoxyl®*, *Ulcaid®*, *Zantac®*,

**Class:** Histamine-2 receptor antagonist (H2RA).

**Licensed indications:** duodenal ulcer, gastric ulcer, reflux oesophagitis, dyspepsia.

**Recognised other use(s) in palliative care:** itch, sweating, administration by subcutaneous injection or infusion for any clinical indication.

**Contraindications/cautions:** proven allergy to ranitidine.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* accumulation may occur in severe renal impairment; consider dose reduction.

**Adverse reactions:**

*Common:* diarrhoea, tiredness.

*Less common:* blurred vision, gynaecomastia, bradycardia, tachycardia, hypotension, agitation, hallucinations, blood disorders, dizziness, headache, confusion.

**Interactions:**

Ranitidine may decrease the absorption and effect of ketoconazole.

**Dosage:**

*Oral:* 150mg twice a day or 300mg at night (reduce dose in elderly and renal impairment).

*SC:* 100-200mg/24 hours.

**Syringe driver:** refer to syringe driver compatibility chart.

**Mechanism of action:** inhibits gastric acid secretion via blockade of histamine-2 receptors in parietal cells.

**Onset:** of action typically 10 to 60 minutes after oral dosing.

**Peak:** of action not reported; however peak plasma levels typically 2 to 3 hours after oral dosing.

**Duration:** of action around 8 to 12 hours; half-life 2 to 3 hours.

**Availability:**

*Tablets:*

150mg, PBS general benefit [60](5)

*Tablets (effervescent):*

150mg, PBS general benefit [60](5)

*Tablets:*

300mg, PBS general benefit [30](5)

*Oral Liquid:*

15mg/mL, PBS general benefit [600mL](5)

*Injection:*

10mg/mL 5 mL, Not PBS funded

25mg/mL 2 mL, Not PBS funded

Ranitidine preparations are available from a range of manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- Proton Pump Inhibitors (e.g. omeprazole, esomeprazole or pantoprazole) are considered the drugs of choice for prophylaxis or treatment of NSAID-induced GI damage, rather than histamine-2 receptor antagonists.

## **RIFAMPICIN**

Rifadin®, Rimycin®

**Class:** Antibiotic – rifamycin.

**Licensed indications:** tuberculosis (in combination with other drugs), other mycobacterial infections (e.g. *M. ulcerans*), MRSA infection (in combination with other drugs), leprosy, selected serious or prosthesis-associated infection (in combination with other anti-staphylococcal agents), prophylaxis for close contacts of people with meningococcal disease, *H. influenzae* type b disease.

**Recognised other use(s) in palliative care:** pruritus in chronic cholestasis.

**Contraindications/cautions:** proven allergy to rifampicin or any other rifamycin antibiotic, combination with other hepatotoxic drugs, jaundice (seek specialist advice, see notes below).

### **Specific considerations:**

*Hepatic impairment:* rifampicin may worsen hepatic impairment, use cautiously; a lower dose may be necessary.

*Renal impairment:* not reported to require dose adjustment in renal impairment.

### **Adverse reactions:**

Immunological adverse effects, may be more common when rifampicin is given on an intermittent basis.

*Common:* red or brown discolouration of body fluids, arthralgia and myalgia (in the first weeks), dizziness, headache, drowsiness, confusion, ataxia, fatigue and weakness may occur.

*Less common:* self-limited flushing and itching, hepatotoxicity.

### **Interactions:**

Rifampicin is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of rifampicin may be increased by cytochrome inhibitors:  
e.g. ketoconazole.

Concentrations and effect of rifampicin may be decreased by cytochrome inducers:  
e.g. phenobarbitone.

Additive effects with other hepatotoxic drugs, including paracetamol.

Rifampicin is also a potent inducer of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a high risk of clinically significant interactions:

Rifampicin may induce the metabolism and decrease the concentration and effect of:  
amitriptyline, buprenorphine, clonazepam, codeine, dexamethasone, diazepam, fentanyl, fluconazole, haloperidol, ketoconazole, methadone, metronidazole, mexiletine, midazolam, mirtazapine, morphine, nitrazepam, nortriptyline, ondansetron, oxycodone, phenobarbitone, prednisolone, phenytoin, rifampicin, warfarin, zopiclone.

### **Dosage:**

Pruritus associated with chronic cholestasis:

*Oral:* up to 600mg per day in two divided doses.

Refer to AMH for the dosage appropriate for other clinical indications.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** in cholestasis two mechanisms of action for Rifampicin have been proposed: 1) induction of hepatic enzyme activity leading to increased metabolism of endogenous pruritogenic compounds 2) inhibition of hepatocyte bile salt uptake leading to reduction in bile salt mediated disruption of hepatocyte membranes which causes the release of “pruritogens”. Rifampicin exerts its antibacterial action by inhibiting DNA-dependent RNA polymerase activity in susceptible bacterial cells.

**Onset:** of action variable.

**Peak:** of action not reported; however plasma levels peak around 2 to 4 hours after oral dosing.

**Duration:** of action not reported; however half life initially in range of 2 to 5 hours, decreasing with longer term use to 2 to 3 hours.

**Availability:**

*Tablets:*

600mg, Not PBS funded

*Capsules:*

150mg, PBS authority benefit [100](0)<sup>1</sup> [10](0)<sup>2</sup>

300mg, PBS authority benefit [100](0)<sup>1</sup>[10](0)<sup>2</sup>

*Oral liquid:*

20mg/mL, [60 mL](0)<sup>2</sup>

*Injection (powder and solvent):*

600mg, Not PBS funded

Rifampicin preparations from different manufacturers may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. Authority benefit for leprosy in adults.
2. Restricted benefit for prophylaxis of meningococcal disease in close contacts and carriers; prophylactic treatment of contacts of patients with *Haemophilus influenzae* type B.

**Notes:**

- rifampicin is potentially hepatotoxic, it is usually recommended to obtain baseline LFTs and monitor these during treatment. However, when used for pruritus in palliative care, these recommendations need to be considered mindful that the relative risks and benefits may be different.

## **RISPERIDONE**

Risperdal®

**Class:** Antipsychotic – atypical.

**Licensed indications:** schizophrenia and related psychoses, behaviour disturbance in dementia, conduct and other disruptive behaviour disorders in adults and children over 5 years with sub-average intellectual functioning or mental retardation, short term treatment of acute mania, behavioural disorders in children and adolescents with autism.

**Recognised other use(s) in palliative care:** delirium.

**Contraindications/cautions:** proven allergy to risperidone, Parkinson's disease, epilepsy, cardiovascular disease.

**Specific considerations:**

*Hepatic impairment:* use half the usual starting and incremental doses.

*Renal impairment:* dose reduction may be required.

**Adverse reactions:**

*Common:* insomnia, anxiety, headache.

*Less common:* drowsiness, dizziness, gastro-intestinal upset, sexual dysfunction, constipation, dry mouth, postural hypotension.

**Interactions:**

Risperidone is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of risperidone may be increased by cytochrome inhibitors: e.g. fluoxetine.

Concentration and effect of risperidone may be decreased by cytochrome inducers: e.g. carbamazepine, phenobarbitone, phenytoin and rifampicin.

Risk of dyskinesia increased by methylphenidate.

Additive effects with other CNS depressant drugs.

Additive effects with other drugs that cause hypotension.

Additive effects with other drugs that cause extra-pyramidal effects.

Risperidone may increase levels and effect of carbamazepine.

**Dosage:**

Delirium (Note: 2<sup>nd</sup> line treatment, non-sedating, for mild to moderate symptoms, by oral route only, have to be willing and able to swallow):

*Oral:* 0.25-0.5mg twice a day regularly, plus additional as required doses of 0.25mg (given up to of 4 times per 24 hours), i.e. dose range over 24 hours 0.5-3mg.

Psychosis:

*Oral:* 0.5-4mg twice a day.

Behaviour disturbance in dementia:

*Oral:* 0.25mg twice daily, increasing according to response by 0.25mg daily every 2 or more days, usual range 0.5-1mg twice daily.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** selective monoaminergic antagonist with a high affinity for both serotonergic 5-HT<sub>2</sub> and dopaminergic D<sub>2</sub> receptors. Risperidone also binds to alpha-1 adrenergic receptors and with lower affinity to histamine-1 and alpha-2 adrenergic receptors.

**Onset:** of action 1 to 2 weeks in psychosis, hours to days in delirium.

**Peak:** of action not reported; however plasma levels peak within 1 to 2 hours of oral dosing.

**Duration:** of action variable from 12 to 48 hours; half-life of the active antipsychotic fraction is 24 hours.

**Availability:**

*Tablets:*

0.5mg, PBS authority benefit [60](5)<sup>1</sup> [60](2)<sup>3</sup>

1mg, PBS authority benefit [60](5)<sup>2</sup> [60](2)<sup>3</sup>

2mg, PBS authority benefit [60](5)<sup>2</sup> [60](2)<sup>4</sup>

3mg, PBS authority benefit [60](5)<sup>2</sup>

4mg, PBS authority benefit [60](5)<sup>2</sup>

*Tablets (orally disintegrating):*

0.5mg, PBS authority benefit [56](5)<sup>1</sup> [56](2)<sup>3</sup>

1mg, PBS authority benefit [56](5)<sup>2</sup>[56](2)<sup>3</sup>

2mg, PBS authority benefit [56](5)<sup>2</sup>

3mg, PBS authority benefit [56](5)<sup>2</sup>

4mg, PBS authority benefit [56](5)<sup>2</sup>

*Oral liquid:*

1mg/mL, 30 & 100 mL, PBS authority benefit [100mL](5)<sup>2</sup> [30ml](2)<sup>3</sup>

Different risperidone preparations may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. PBS authority for schizophrenia.
2. PBS authority for schizophrenia and as adjunctive therapy to mood stabilisers for up to 6 months, of an episode of acute mania associated with bipolar I disorder.
3. PBS authority for behavioural disturbances characterised by psychotic symptoms and aggression in patients with dementia where non-pharmacological methods have been unsuccessful; treatment under the supervision of a paediatrician or psychiatrist, in combination with non-pharmacological measures, of severe behavioural disturbances in a child or adolescent aged less than 18 years with autism. Behaviour disturbances are defined as severe aggression and injuries to self or others where non-pharmacological methods alone have been unsuccessful. The diagnosis of autism must be made based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or ICD-10 international classification of mental and behavioural disorders.
4. treatment under the supervision of a paediatrician or psychiatrist, in combination with non-pharmacological measures, of severe behavioural disturbances in a child or adolescent aged less than 18 years with autism. Behaviour disturbances are defined as severe aggression and injuries to self or others where non-pharmacological methods alone have been unsuccessful. The diagnosis of autism must be made based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or ICD-10 international classification of mental and behavioural disorders.

**Notes:**

- risperidone has a lower potential for neurological adverse effects than conventional (“typical”) antipsychotics.
- at high dose (> 6-8mg per day) or in the cerebrally compromised patient, extra pyramidal side-effects still may occur.

- increasingly used in acute delirium and behavioural disturbances associated with brain tumours.

## SALIVA REPLACEMENTS

Various including: *Aquae*®, *Biotene Oralbalance*®, *Oralube*®

**Class:** Saliva replacements

**Licensed indications:**

*Aquae*®: to moisten the mucosa of the mouth, tongue and throat.

*Biotene Oralbalance*®: for relief of severe dry mouth symptoms, burning, sore tissues, cotton palate, bad breath, swallowing and denture wearing difficulties.

*Oralube*®: to treat the symptoms of dry mouth and salivary gland hypofunction.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to constituents.

**Specific considerations:**

*Hepatic impairment:* not expected to require change in use.

*Renal impairment:* not expected to require change in use.

**Adverse reactions:**

Rarely reported, these preparations are generally well tolerated.

**Interactions:** none reported.

**Dosage:**

*Aquae*®: *Aquae* should be held 2 to 3cm from the mouth and aimed carefully. Spray 1 to 2 times into the mouth, or as directed, may be used as often as needed.

*Biotene Oralbalance*®: apply to gums and tongue as required.

*Oralube*®: one to two puffs of spray directed into the back of the mouth and tongue when required.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** oral lubricant.

**Onset:** of action almost immediate.

**Peak:** of action not applicable.

**Duration:** of action not applicable.

**Availability:**

*Aquae*®: 25mL and 100mL, Palliative Care authority [1](3)<sup>1</sup> [1](0)<sup>2</sup>

*Biotene Oralbalance*®: Not PBS funded

*Oralube*®: Not PBS funded

Different preparations contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. Initial supply (for up to 4 months) for palliative care patients where dry mouth is a symptom; continuing supply for palliative care patients where dry mouth is a symptom and where consultation with a palliative care specialist or service has occurred.
2. Continuing supply for palliative care patients where dry mouth a symptom.

**Notes:** none.

## SENNA

*Sennatabs®*, *Senokot®*, *Laxettes with Senna®*, (combination: *Coloxyl with Senna®*)

**Class:** Laxative – stimulant.

**Licensed indications:** constipation.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to senna, acute abdominal pain, intestinal obstruction, inflammatory bowel disease.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* not reported to require dose adjustment.

**Adverse reactions:**

*Common:* abdominal cramps, diarrhoea, perianal irritation.

*Less common:* atonic colon (with prolonged use), hypokalaemia, brown or pink discolouration of urine.

**Interactions:**

May potentially antagonise the effects of antispasmodics e.g. hyoscine butylbromide.

**Dosage:**

*Oral (Senna single agent preparation):* 2 to 4 tablets (or equivalent) at night.

*Oral (Docusate with senna preparation):* 1 to 2 tablets at night, maximum 4 tablets.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** stimulates colonic activity via nerves in the intestinal mucosa; may also have stool softening properties through accumulation of water and electrolytes in the colonic lumen.

**Onset:** of action 6 to 12 hours.

**Peak:** of action 6 to 12 hours.

**Duration:** of action not applicable.

**Availability:**

*Tablets:*

7.5mg, RPBS benefit only.

12mg, Not PBS funded.

*Granules:*

5.5mg/g, Not PBS funded.

*Squares:*

12mg, Not PBS funded.

Different Senna preparations contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- may be useful in opioid induced constipation.

## SODIUM BICARBONATE

Sodium Bicarbonate Mouthwash, Oraswab®

**Class:** Alkalinising agent.

**Licensed indications:** used to alleviate bad breath and to help relieve mouth ulcers (Orion product), to clean and lift debris and mucus (Oraswab®).

**Recognised other use(s) in palliative care:** any uses of extemporaneous preparations and uses other than those above (for Orion product and Oraswab®).

**Contraindications/cautions:** proven allergy to constituents of the preparation used, when used as a mouthwash solution sodium bicarbonate should be expelled from the mouth where possible. If swallowed, the following cautions apply: should not generally be given to patients with metabolic or respiratory alkalosis, hypocalcaemia or hypochlorhydria; should be given with extreme caution to patients with heart failure, oedema, renal impairment, hypertension, eclampsia or aldosteronism. Some commercially available products (e.g. Orion product) contain ethanol which may exacerbate a sore or tender mouth.

**Specific considerations:**

*Hepatic impairment:* not reported to require change in use.

*Renal impairment:* not applicable unless Sodium Bicarbonate solution is swallowed, when caution in renal impairment is required.

**Adverse reactions:**

Generally well tolerated when used as mouthwash solution, although the ethanol content of some products may exacerbate a sore or tender mouth.

*Less common (Note: only a risk where swallowed):* hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function; symptoms include mood changes, tiredness, slow breathing, muscle weakness, and irregular heartbeat.

**Interactions:** When used as a mouthwash solution sodium bicarbonate should be expelled from the mouth where possible. If swallowed, the reduction of gastric acidity and alkalinisation of urine may affect the absorption and elimination of certain drugs; seek further advice in such cases.

**Dosage:**

*Mouthwash (Orion):* 15-30mL as required, rinsed around mouth and expelled.

*Mouthwash (Extemporaneous: one teaspoon of Sodium Bicarbonate per 500-600mL of water):* used as required, rinsed around mouth and expelled.

*Oraswab®:* dip the swab into warm water, express excess liquid and then use the swab to clean the teeth, buccal cavity, hard palate and tongue.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** Sodium bicarbonate is an alkalinising agent which acts as an oral cleanser by deodorising and buffering activity.

**Onset:** of action almost immediate.

**Peak:** of action not applicable.

**Duration:** of action not applicable.

**Availability:**

*Mouthwash Solution 1% (Orion Laboratories);* 200mL and 500mL – Not PBS funded.

*Oraswab® X76065 (Confident Care Products)* – Not PBS funded.

*Extemporaneously prepared*– Not PBS funded.

Different preparations contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:** none.

## **SPIRONOLACTONE**

*Aldactone®*, *Spiractin®*

Class: Diuretic – potassium sparing, aldosterone antagonist.

Licensed indications: primary hyperaldosteronism, refractory oedema associated with secondary hyperaldosteronism, hirsutism in females.

Recognised other use(s) in palliative care: malignant ascites, severe heart failure.

Contraindications/cautions: proven allergy to spironolactone, hyperkalaemia, hyponatraemia.

Specific considerations:

*Hepatic impairment*: not reported to require dose adjustment in hepatic impairment.

*Renal impairment*: increased risk of hyperkalaemia, caution in mild to moderate renal impairment, avoid in severe renal impairment.

Adverse reactions:

*Common*: gastro-intestinal upset, drowsiness, hyperkalaemia.

*Less common*: rashes, headache, confusion, impotence, gynaecomastia, hyponatraemia.

Interactions:

Effects of spironolactone enhanced by other diuretics.

Effects of spironolactone may be reduced by NSAIDs.

Additive effects with other drugs that cause hyperkalaemia.

Dosage:

Malignant ascites:

*Oral*: usually 25–200mg once daily, maximum 400mg daily.

Oedema:

*Oral*: initially 100mg once daily; maintenance 25–200mg daily.

Primary hyperaldosteronism:

*Oral*: 50–200mg once daily.

Syringe driver: not given parenterally, therefore not applicable.

Mechanism of action: inhibits action of aldosterone leading to natriuresis and retention of potassium.

Onset: of action 2 to 4 hours.

Peak: of action 6 to 8 hours as aldosterone antagonist, 10 to 25 days to reduce ascites; plasma levels peak after 2 to 3 hours.

Duration: of action around 24 hours for single doses, increasing to 2 to 3 days for multiple dosing.

Availability:

*Tablets (scored)*:

25mg, PBS general benefit [100](5)

100mg, PBS general benefit [100](5)

Different spironolactone preparations may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

Notes:

- paracentesis may be necessary in malignant ascites.
- monitor body weight and renal function.

## SUFENTANIL

Sufenta®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid (quick acting, short duration).

**Licensed indications:** short duration analgesic used in anaesthesia generally in epidural procedures.

**Recognised other use(s) in palliative care:** use for management of incident (short duration, high intensity pain); administration by subcutaneous injection or infusion, or by buccal or intranasal routes for any clinical indication (all specialist use only).

**Contraindications/cautions:** proven allergy to sufentanil or fentanyl.

Note: past nausea or hallucinations with opioids are not contraindications.

### **Specific considerations:**

*Hepatic impairment:* limited data available, use with caution.

*Renal impairment:* limited data available, use with caution.

**Adverse reactions:** All opioids share a common range of adverse effects, although these are dose dependent and affected by circumstances of use. There is however significant variation between individuals in their response to different opioids and the different opioids have metabolites which may add to the adverse effects. Switching (rotating) to another, chemically distinct, opioid may therefore be useful to reduce adverse effects by allowing a wash out of these metabolites and presenting the mu receptors with a "fresh" opioid configuration.

**Constipation occurs in up to 90% of patients on opioids, always ensure there is a bowel control plan with laxatives.**

Nausea and vomiting are usually transient in the first few (1-5) days and may require metoclopramide or haloperidol to prevent symptoms. Transient confusion and sedation are also common, if persistent they will necessitate a reduction in the opioid dose or switching to another opioid. Dry mouth, dizziness and visual difficulty (particularly problems with accommodation) are also common.

*Less Common:* respiratory depression (usually only at high doses but does occur in the opioid naive when there is no titration of dosage, naloxone can reverse respiratory depression but will also reverse analgesia), myoclonic jerking, delirium, pruritus.

Respiratory depression is a serious side effect of opioids but is a symptom which is uncommon in Palliative Medicine where titration of opioids to pain or breathlessness is the norm. Respiratory rate reduction is often a late manifestation of opioid toxicity, but sedation is a better indicator and can be monitored by using a sedation score such as:

<b>Sedation Score</b>	
Score	Sedation level
0	wide awake
1	easy to rouse
2	easy to rouse, but cannot stay awake
3	difficult to rouse
With opioids, the aim is to keep sedation to a level of less than 2 on this scale.	

Adverse effects, including respiratory depression, will persist for longer if there has been accumulation of sufentanil, extended monitoring may therefore be required.

*Rare:* visual hallucinations, hyperalgesia, biliary/urinary tract spasm, physical dependence (irrelevant in palliative care), SIADH, anaphylaxis, seizure.

**Interactions:**

Sufentanil is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. Although there are few reports of interactions specifically affecting sufentanil, some of the interactions known to affect fentanyl and related drugs may apply to sufentanil. However, in the absence of data specific to sufentanil, concerns about these interactions should not deter efforts to optimise symptom control where appropriate.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

**Dosage:**

Sufentanil should only be used under specialist advice. Sufentanil is a very potent analgesic, about 5 to 10 times more potent than fentanyl and 400 to 800 times more potent than morphine. There is incomplete and variable cross tolerance along with significant individual variation in response and there is no known consistent equivalent dose ratio when using sufentanil for incident pain. Incremental titration is required for each patient. Sufentanil is denatured by gastric acid so when given by relevant routes the patient should be instructed not to swallow for 2 minutes.

*Sublingual:* seek specialist advice.

*Intranasal:* seek specialist advice.

*SC:* seek specialist advice.

**Syringe driver:** seek specialist advice.

**Onset:** of action *Intranasal:* variable, typically 3 to 20 minutes; *Sublingual:* not reported.

**Peak:** of action *Intranasal:* variable, typically around 20 minutes; *Sublingual:* not reported.

**Duration:** of action variable, typically 20 to 40 minutes; half-life is around 2.5 hours.

**Mechanism of action:** sufentanil is a very potent opioid analgesic with strong mu receptor affinity, it is highly lipid soluble and absorbed through mucous membranes.

**Availability:**

*Injection:*

0.05mg/mL 1 & 5 mL, Not PBS funded; via Special Access Scheme – Category A. **Notes:**

- paracetamol and an NSAID are effective co-analgesics when given with opioids in the treatment of bone and soft tissue pain.
- sufentanil is non irritant when given subcutaneously.
- the high potency and low volume of sufentanil means that it can be a useful alternative to morphine or other opioids in a syringe driver where volume conservation is important.

## TEMAZEPAM

Normison®, Temtabs®, Temaze®

**Class:** Benzodiazepine – hypnotic.

**Licensed indications:** short term treatment of insomnia.

**Recognised other use(s) in palliative care:** longer term use, see PBS notes.

**Contraindications/cautions:** proven allergy to temazepam, avoid sudden withdrawal, respiratory depression, myasthenia gravis, elderly.

**Specific considerations:**

*Hepatic impairment:* contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present. In mild-to-moderate impairment, use low doses of a short acting benzodiazepine to reduce risk of precipitating coma.

*Renal impairment:* increased sensitivity to CNS effects in renal impairment, use a lower initial dose in severe impairment.

**Adverse reactions:**

*Common:* drowsiness, excess sedation, memory loss, light-headedness, ataxia, hypersalivation, slurred speech.

*Less common:* disorientation, confusion, headache, vertigo, paradoxical excitation, euphoria, aggression and hostility, anxiety, decreased libido, anterograde amnesia, respiratory depression, hypotension.

**Interactions:**

Temazepam is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. Although there are few reports of interactions specifically affecting temazepam, some of the interactions known to affect other benzodiazepines e.g. diazepam or midazolam may apply to temazepam. However, in the absence of data specific to temazepam, concerns about these interactions should not deter efforts to optimise symptom control where appropriate.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Benzodiazepines may increase or decrease the concentration and effect of phenytoin.

**Dosage:**

*Oral:* 5–20mg at night, elderly initially 5–10 mg at night.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** potentiates the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the CNS, resulting in anxiolytic, sedative, hypnotic, muscle relaxant and antiepileptic effects.

**Onset:** of action within 30 to 60 minutes.

**Peak:** of action not reported; however plasma levels peak after 30 minutes to 2 hours.

**Duration:** of action not reported; however half-life is around 8 to 15 hours.

**Availability:**

*Tablets:*

10mg, PBS general benefit [25](0), PBS authority benefit [50](5)<sup>1</sup>, PBS palliative care authority benefit [50](3)<sup>2</sup>, PBS authority benefit [50](0)<sup>3</sup>

Different temazepam preparations may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. malignant neoplasia (late stage); for use by patients who are receiving long-term nursing care on account of age, infirmity or other condition in hospitals, nursing homes or residential facilities and who have been demonstrated, within the past 6 months, to be benzodiazepine dependent by an unsuccessful attempt at gradual withdrawal; for use by a patient who is receiving long-term nursing care and in respect of whom a Carer Allowance is payable as a disabled adult and who has been demonstrated, within the past 6 months, to be benzodiazepine dependent by an unsuccessful attempt at gradual withdrawal.
2. initial supply (for up to 4 months) for palliative care patients where insomnia is a problem; continuing supply for palliative care patients where insomnia is a problem and where consultation with a palliative care specialist or service has occurred.
3. continuing supply for palliative care patients where insomnia is a problem.

**Notes:**

- See below for comparison with other benzodiazepines and zopiclone.

<b>Pharmacological properties and dose equivalents* for benzodiazepines and zopiclone</b>					
Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## TRAMADOL

Tramahexal®, Tramahexal SR®, Tramal®, Tramedo®, Tramedo SR®, Zydol®

**The Palliative Care Service recommends Morphine as the preferred opioid analgesic for moderate to severe pain because of familiarity, availability and cost. Other opioids may be used where adverse effects of morphine are unacceptable.**

**Class:** Analgesic – opioid-like (with additional effects on inhibitory pain pathways).

**Licensed indications:** moderate to severe pain.

**Recognised other use(s) in palliative care:** administration by subcutaneous injection for any clinical indication.

**Contraindications/cautions:** proven allergy to tramadol, epilepsy, drug abuse, respiratory depression.

Note: past nausea or hallucinations with opioids are not contraindications.

### **Specific considerations:**

*Hepatic impairment:* in severe hepatic impairment do not use controlled release formulation, reduce dose of parenteral and standard oral formulations.

*Renal impairment:* excretion decreased in renal impairment, reduce dose if creatinine clearance <30 mL/minute; avoid if <10 mL/minute.

### **Adverse reactions:**

*Common:* nausea, vomiting, diarrhoea, sweating (dose related).

*Less common:* dry mouth, sedation, headache, hypertension, confusion.

### **Interactions:**

Tramadol is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. However, the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate.

Ondansetron may reduce the analgesic effect of tramadol.

Additive effects with other CNS depressant drugs.

Additive effects with other respiratory depressant drugs.

Additive effects with other serotonergic drugs, increasing risk of serotonin syndrome.

Additive effects with other drugs that lower seizure threshold.

Tramadol may increase effect of warfarin.

### **Dosage:**

Start with low dose to minimise adverse effects and titrate to response, maximum of 400mg/24 hours.

*Oral:* 50–100mg 4-6 hourly.

*Oral (controlled release):* 100-200mg twice a day.

*SC:* up to 400mg/24 hours.

**Syringe driver:** not applicable.

**Mechanism of action:** stimulates opioid ( $\mu$ ) receptors in CNS and GIT and also affects noradrenaline and serotonin in descending spinal inhibitory pain pathways.

**Onset:** of action *Oral (normal release):* 30 to 60 minutes.

**Peak:** of action not reported; however peak plasma levels *Oral (normal release):* 0.5 to 1 hour, *Oral (Tramahexal CR):* around 5 hours.

**Duration:** of action *Oral (normal release):* 3 to 7 hours, *Oral (Tramahexal CR):* around 12 hours.

**Availability:**

*Capsules:*

50mg, PBS restricted benefit [20](0)<sup>1</sup>

*Tablets (controlled release):*

50mg, PBS Restricted benefit[20](0)<sup>2</sup>

100mg PBS restricted benefit[20](0)<sup>2</sup>

150mg, PBS restricted benefit[20](0)<sup>2</sup>

200mg, PBS restricted benefit[20](0)<sup>2</sup>

*Oral liquid:*

100mg/mL (50 mg/20 drops), PBS restricted benefit [10ml](0)<sup>2</sup>

*Injection:*

50mg/mL 2 mL, PBS restricted benefit [5](0)<sup>3</sup>

Different tramadol preparations may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

1. For acute pain where aspirin and/or paracetamol alone are inappropriate or have failed.
2. For pain where aspirin and/or paracetamol alone are inappropriate or have failed.
3. Short-term treatment of acute pain.

**Notes:**

- paracetamol and an NSAID are effective co-analgesics when given with opioids such as tramadol in the treatment of bone and soft tissue pain.
- the place of tramadol in palliative care is still to be established.
- tramadol may be useful in patients where codeine or morphine have caused problematic constipation.
- controlled release preparations of tramadol may be better tolerated due to reduced fluctuations in blood levels.
- 6 to 10% of Caucasians and 1 to 2% of Asians lack the enzyme necessary for the metabolism of tramadol to the active metabolite O-desmethyltramadol.
- naloxone only partially reverses tramadol overdose and may increase the risk of seizures.
- tramadol is not a controlled drug.

# TRANEXAMIC ACID

Cyklokapron®

**Class:** Antifibrinolytic.

**Licensed indications:** haemorrhage, surface bleeding from tumours, nose and other organs; prevention of hereditary angioedema; prevention of haemorrhage in patients with mild-to-moderate coagulopathies undergoing minor surgery; menorrhagia; hyphaema.

**Recognised other use(s) in palliative care:** topical use (seek specialist advice).

**Contraindications/cautions:** proven allergy to tranexamic acid, active clotting, urinary tract bleeds, subarachnoid haemorrhage.

**Specific considerations:**

*Hepatic impairment:* not reported to require dose adjustment.

*Renal impairment:* reduce dose in renal impairment; in haematuria due to renal parenchymal disease thrombosis may lead to intrarenal obstruction.

**Adverse reactions:**

*Common:* nausea, vomiting, diarrhoea.

*Less common:* dizziness (with IV), thrombocytopenia, headache, restlessness.

**Interactions:**

Tranexamic acid may antagonise anticoagulants.

**Dosage:**

*Oral:* 500mg-1500mg 3 to 4 times a day.

*Topical:* seek specialist advice - solutions have been used topically on bleeding wounds and as a mouth wash.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** inhibits the breakdown of clots by blocking the binding of plasminogen and plasmin to form fibrin.

**Onset:** of action within 1 to 3 hours of oral dosing.

**Peak:** of action not reported; however plasma levels peak within 3 hours of oral dosing.

**Duration:** of action around 24 hours; half-life is around 2 hours.

**Availability:**

*Tablets:* 500mg, PBS general benefit [100](2)

*Injection:* 500mg/5mL, not marketed in Australia but via Special Access Scheme

Currently only available as the brand Cyklokapron®.

**Note:**

- care should be taken if crushing tablets to produce a mouthwash to minimise exposure of the individual and contamination of the product.

## VALPROATE SODIUM (SODIUM VALPROATE)

Epilim®, Valpro®, Valproate®

**Class:** Anticonvulsant.

**Licensed indications:** primary generalised epilepsy (including absence, tonic-clonic, myoclonic and atonic seizures) and simple and complex partial seizures; bipolar disorder when other treatments have failed.

**Recognised other use(s) in palliative care:** neuropathic pain, prevention of migraine when other treatments have failed.

**Contraindications/cautions:** proven allergy to valproic acid and its salts, porphyria, pancreatic dysfunction.

**Specific considerations:**

*Hepatic impairment:* avoid if possible, hepatotoxicity and hepatic failure may occur. Contraindicated in severe hepatic impairment.

*Renal impairment:* doses should be reduced in renal impairment.

**Adverse reactions:**

*Common:* gastro-intestinal upset, tremor, weight gain, drowsiness, ataxia.

*Less common:* thrombocytopenia, transient hair loss, hepatotoxicity.

**Interactions:**

Valproate is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system. With the exception of other anticonvulsants, the literature contains few references to clinically significant interactions affecting valproate, therefore concerns about such interactions should not deter efforts to optimise symptom control where appropriate (see below for the effect valproate may have on other drugs).

Various interactions have been reported when valproate is given with other anticonvulsants that induce or inhibit the Cytochrome P450 system e.g. carbamazepine, phenytoin and phenobarbitone.

Cholestyramine may decrease absorption of valproate sodium.

Valproate is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, where these drugs have a narrow therapeutic range, there is a risk of clinically significant interactions:

Valproate may inhibit the metabolism and increase the concentration and effect of: amitriptyline, diazepam, methylphenidate, midazolam, nortriptyline, warfarin.

**Dosage:**

**Epilepsy:**

*Oral:* 15mg/kg daily in 1 or 2 doses; increase every 2 weeks by 200mg daily according to response.

**Neuropathic pain:**

*Oral:* 200–1000mg twice a day.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** prevents repetitive neuronal discharge by blocking voltage dependent and use-dependent sodium channels.

**Onset:** of action variable.

**Peak:** of action not reported; however peak plasma levels with *Oral (EC tablets)* 3 to 7 hours.

**Duration:** of action not reported; half-life reported to range from 8 to 17 hours.

**Availability:**

*Tablets (scored, crushable):*

100mg, PBS general benefit [200](2)

*Tablets (enteric coated):*

200mg, PBS general benefit [200](2)

500mg, PBS general benefit [200](2)

*Oral Liquid:*

40mg/mL 300 mL, PBS general benefit [600mL](2)

*Injection (powder and solvent):*

400mg, Not PBS funded

Different Valproate sodium preparations may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- co-analgesic often used with opioids in the treatment of neuropathic pain.
- may be used in neuropathic pain when tricyclic antidepressants have failed or in combination with tricyclic antidepressants.
- gabapentin may be more effective in neuropathic pain.
- when switching from carbamazepine to sodium valproate, watch for toxicity from other drugs; carbamazepine induces the metabolism of other drugs while sodium valproate inhibits the metabolism of other drugs.
- do not discontinue abruptly due to risk of rebound seizures.
- therapeutic drug monitoring is usually of limited clinical value.
- monitor LFTs.

## VENLAFAXINE

Efexor XR®

**Class:** Antidepressant - Serotonin and noradrenaline reuptake inhibitor (SNRI).

**Licensed indications:** major depression, generalised anxiety disorder, panic disorder, social phobia.

**Recognised other use(s) in palliative care:** neuropathic pain.

**Contraindications/cautions:** proven allergy to venlafaxine, current or recent (within 14 days) MAOI therapy or within 2 days of stopping moclobemide.

**Specific considerations:**

*Hepatic impairment:* halve dose in severe impairment.

*Renal impairment:* halve dose in severe impairment and in haemodialysis patients.

**Adverse effects:**

*Common:* nausea, vomiting, anorexia, headache, sweating, rash, anxiety, dizziness, fatigue, hypertension (dose related), tremor.

*Infrequent:* dry mouth, insomnia, somnolence, constipation, sexual dysfunction, hyponatraemia, orthostatic hypotension, syncope.

*Rare:* skin and mucous membrane bleeding, glaucoma, seizures, hepatitis.

**Interactions:**

Venlafaxine is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that affect this system:

Concentration and effect of venlafaxine may be increased by cytochrome inhibitors:  
e.g. fluconazole, ketoconazole.

Additive effects with other drugs that cause sedation.

Additive effects with other serotonergic drugs, increasing risk of serotonin syndrome.

Venlafaxine is also an inhibitor of the Cytochrome P450 system involved in the metabolism of other drugs, however its effects are reported to be weak; therefore the clinical significance of such interactions is generally low and concerns about these should not deter efforts to optimise symptom control where appropriate (see above for the effect other drugs may have on venlafaxine).

**Dosage:**

*Oral:* 37.5mg once daily, increasing to 150mg once daily, some patients may respond to a further increase in the dose to 225mg once daily.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** inhibits re-uptake of serotonin and noradrenaline within CNS.

**Onset:** of action minimum of 14 days.

**Peak:** of action not reported; however peak plasma levels with *Oral (CR capsules)* 4.5 to 7.5 hours.

**Duration:** of action not reported; however half-life of venlafaxine is around 5 hours, note that this will effectively be extended in clinical practice due to the use of the more slowly absorbed CR preparations.

**Availability:**

*Capsules (controlled release):*

37.5mg, PBS restricted benefit [28](0)

75mg, PBS restricted benefit [28](5)

150mg, PBS restricted benefit [28](5)

PBS notes:

restricted benefit for major depressive disorders.

**Notes:**

- allow at least 7 days after stopping venlafaxine before starting an MAOI.
- venlafaxine CR capsules should not be crushed.

## **WARFARIN**

*Coumadin®*, *Marevan®*

**Note:** when an anticoagulant is indicated in palliative care, low molecular weight heparins (e.g. enoxaparin) are generally preferred to warfarin as maintaining a stable INR can be problematic due to changes in body weight, dietary intake and clotting pathways associated with disease processes.

**Class:** Oral anticoagulant – coumarin.

**Licensed indications:** prophylaxis and treatment of thrombotic disorders.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to warfarin – consider cross sensitivity with other coumarin anticoagulants, potential haemorrhagic conditions, sudden and significant changes to diet may lead to altered anticoagulant effect, any changes in drug therapy should be accompanied by an INR check.

**Specific considerations:**

*Hepatic impairment:* use with caution due to increased risk of bleeding.

*Renal impairment:* use with caution due to increased risk of bleeding.

**Adverse reactions:**

*Common:* bleeding.

*Less common:* hair loss, fever, nausea, vomiting, diarrhoea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

*Rare:* purple toe syndrome.

**Interactions:**

Warfarin is metabolised by the Cytochrome P450 system and has a narrow therapeutic range, there is therefore a high risk of clinically significant interactions when it is prescribed with drugs that inhibit or induce this system.

Concentration and effect of warfarin may be increased by some cytochrome inhibitors: cimetidine, esomeprazole, fluconazole, fluoxetine, ketoconazole, methylphenidate, metronidazole, miconazole, octreotide, omeprazole, valproate and venlafaxine.

Concentration and effect of warfarin may be decreased by some cytochrome inducers: carbamazepine, phenobarbitone, phenytoin, rifampicin and tobacco smoke.

Paracetamol may occasionally increase the effect of warfarin.

Tramadol may increase the effect of warfarin.

Cholestyramine may decrease the absorption and effect of warfarin.

Use in combination with other drugs that cause bleeding increases this risk.

**Dosage:**

*Oral:* adjusted to INR (see below).

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** interferes with vitamin K synthesis affecting clotting factors (II, VII, IX, X) and the antithrombotic factors protein C and Protein S.

**Onset:** of action dependent on loading regime, usually delayed several days.

**Peak:** of action dependent on loading regime; peak plasma levels typically occur within 4 hours.

**Duration:** of action variable; half-life has a mean of 40 hours.

**Availability:***Tablets:*

1mg, PBS general benefit [50](2)

2mg, PBS general benefit [50](2)

3mg, PBS general benefit [50](2)

5mg, PBS general benefit [50](2)

Warfarin preparations are available from different manufacturers and may contain a variety of excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

**Notes:**

- different brands of warfarin are not proven to be therapeutically equivalent.
- in the presence of cancer (especially adenocarcinoma) a stable INR may be difficult to achieve particularly with variable appetite and exercise, it may be more appropriate to use a low molecular heparin e.g. enoxaparin in these circumstances.
- refer to your pathology provider for appropriate INR levels according to condition treated.
- patients should be advised not to suddenly and significantly vary their diet, as this may lead to altered anticoagulant effect, especially where involving foods rich in vitamin K e.g. green leafy vegetables.

## ZOLEDRONIC ACID

Zometa®, Aclasta®

**Class:** Bisphosphonate.

**Licensed indications:** hypercalcaemia, metastatic bone pain, osteoporosis, Paget's disease.

**Recognised other use(s) in palliative care:** prevention and treatment of osteoporosis (including postmenopausal and corticosteroid-induced).

**Contraindications/cautions:** proven allergy to zoledronic acid, hypocalcaemia.

**Specific considerations:**

*Hepatic impairment:* caution advised in severe hepatic impairment.

*Renal impairment:* in hypercalcaemia of malignancy, manufacturer discourages use when creatinine clearance <30 mL/minute, seek specialist advice. In prevention of skeletal-related events, adjust dose when creatinine clearance <60 mL/minute; manufacturer discourages use when creatinine clearance <30 mL/minute.

**Adverse reactions:**

*Less common:* transient flu-like symptoms, slight increase in temperature, fever, hypocalcaemia, transient bone pain, nausea, headache.

*Rare:* osteonecrosis of the jaw (more commonly associated with dental surgery).

**Interactions:**

Additive effects with other nephrotoxic drugs.

Loop diuretics may increase risk of electrolyte disturbance.

**Dosage:**

Bone pain:

*IV infusion:* 4–8mg every 3-4 weeks.

Hypercalcaemia:

*IV infusion:* 4–8mg depending on serum calcium.

Osteoporosis:

*IV infusion:* 5mg once a year.

**Syringe driver:** not given SC, therefore not applicable.

**Mechanism of action:** inhibits bone resorption by inhibiting osteoclasts.

**Onset:** of action in hypercalcaemia 1 to 2 days, in pain up to 14 days.

**Peak:** of action variable.

**Duration:** of action in hypercalcaemia 2 weeks to 3 months, in pain 3 to 4 weeks.

**Availability:**

*Injection:*

0.8mg/mL 5 mL, PBS Section 100 authority required

5mg/100mL, Not PBS funded

Currently only available as the brands Zometa® and Aclasta®.

PBS notes: Section 100 benefits for: Multiple myeloma; bone metastases from breast cancer; bone metastases from hormone-resistant prostate cancer, with demonstration of biochemical progression of disease despite maximal hormonal therapy; treatment of hypercalcaemia of malignancy refractory to anti-neoplastic therapy.

**Notes:**

- can be given at a rate of 4mg over (a minimum of) 15 minutes, i.e. at a faster rate than pamidronate.

## ZOPICLONE

Imovane®, Imrest®

**Class:** Hypnotic – cyclopyrrolone.

**Licensed indications:** short term treatment of insomnia.

**Recognised other use(s) in palliative care:** none.

**Contraindications/cautions:** proven allergy to zopiclone, alcohol intake.

**Specific considerations:**

*Hepatic impairment:* in significant hepatic impairment use initial dose of 3.75mg.

*Renal impairment:* in significant renal impairment use initial dose of 3.75mg.

**Adverse reactions:**

*Common:* taste disturbance (bitter), dry mouth, drowsiness.

*Less common:* nightmares, hallucinations, dyspepsia, angioedema, anaphylactic reaction.

**Interactions:**

Zopiclone is metabolised by the Cytochrome P450 system, interactions may therefore occur when it is prescribed with drugs that inhibit or induce this system:

Concentration and effect of zopiclone may be increased by some cytochrome inhibitors: e.g. cimetidine, fluconazole, ketoconazole.

Concentration and effect of zopiclone may be decreased by some cytochrome inducers: e.g. carbamazepine, phenobarbital, phenytoin, rifampicin.

Use in combination with other drugs that cause sedation increases this risk.

**Dosage:**

*Oral:* 7.5mg at night for up to 4 weeks, reduce to 3.75mg if possible.

In elderly patients, those who are debilitated or have significant respiratory, renal or hepatic impairment, use an initial dose of 3.75mg at night.

**Syringe driver:** not given parenterally, therefore not applicable.

**Mechanism of action:** Potentiates effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the CNS.

**Onset:** of action within 1 hour.

**Peak:** of action not reported; however plasma levels peak within 1.5 to 2 hours.

**Duration:** of action not reported; however half life is around 5 hours.

**Availability:**

*Tablets (scored):*

7.5mg, Repatriation PBS restricted benefit only [30](0)<sup>1</sup>

Different zopiclone preparations may contain different excipients, seek further advice in patients with intolerance or hypersensitivity to excipients.

PBS notes:

Repatriation PBS restricted benefit only for the short-term treatment of insomnia.

**Notes:**

- See below for comparison with benzodiazepines.

**Pharmacological properties and dose equivalents\* for benzodiazepines and zopiclone**

Drug	Approximate Equiv Doses*	Anxiolytic	Night sedation	Muscle relaxant	Anticonvulsant
alprazolam	0.5 mg	++++	+	+	+
clonazepam	0.5 mg	++	+	+	+++
diazepam	5 mg	+++	+	+++	++
flunitrazepam	0.5mg	+	+++	+	++
lorazepam	0.5 mg	+++	++	+	+
midazolam	7.5 mg	+	+++	+	+++
nitrazepam	5mg	++	+++	+	++
temazepam	10 mg	+	+++	+	+
zopiclone	7.5mg	-	+++	-	-

\* These are considered approximate equivalent anxiolytic-sedative doses, however there is no true equivalent dose for the different benzodiazepines due to their profile of effects and durations of action (see monographs), these doses should therefore only serve as a guide and be modified depending on individual patients' circumstances and responses.

## SYRINGE DRIVERS

A syringe driver is a battery-operated pump that administers drugs subcutaneously. Many of the drugs administered via a syringe driver are not licensed for subcutaneous use and the responsibility for their use lies with the prescriber.

Indications for use of a syringe driver:

- severe nausea and/or vomiting
- dysphagia
- severe oral lesions
- non-absorption of oral medication
- unconscious or sedated patient

Relatively little work has been done on the compatibility of drugs in syringe drivers.

Drugs may be added together and then examined visually for evidence of incompatibility, e.g. precipitation. However, non-visual chemical reactions may be occurring leading to the inactivation of one or more of the drugs or the production of a potentially toxic compound. Visual examination is therefore of limited value. However, in the absence of further research, it is the only check available.

Only combine those drugs that are absolutely essential in the syringe for subcutaneous delivery; if there is any doubt, consultation with a drug information pharmacist may guide practice. The possible use of more than one syringe driver should be considered when a number of drugs need to be given via this route.

In addition to incompatibility problems, there are some drugs which should not be given via a syringe driver as they are simply **not appropriate** for subcutaneous administration, due to the risk of local inflammation or necrosis, these include:

- diazepam
- prochlorperazine
- chlorpromazine

Figure 3 summarises the data from a variety of information sources in Australia, New Zealand and the United Kingdom, representing experience and usage with syringe drivers containing combinations of **two** drugs. Please seek advice if uncertain about combinations. As general rule it is recommended that a **maximum of three drugs** be used in combination.

**Figure 3. Summary of compatibility data for two drug combinations in syringe drivers**

	Clonazepam	Cyclizine	Fentanyl	Glycopyrrolate	Haloperidol	Hydromorphone	Hyoscine butylbromide	Hyoscine hydrobromide	Ketamine	Ketorolac	Lignocaine	Methadone	Methotrimeprazine	Metoclopramide	Midazolam	Morphine	Octreotide	Phenobarbitone	Ranitidine	Sodium chloride 0.9%	Sufentanil	Water for injection	
Clonazepam	*	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△	△	N	△	Y	◆	△	
Cyclizine	△	*	N	?	Y	N	N	?	?	N	N	?	Y	Y	?	Y	?	N	?	N	◆	Y	
Fentanyl	△	N	*	Y	Y	*	?	Y	Y	Y	N	*	Y	Y	Y	*	Y	N	?	Y	◆	Y	
Glycopyrrolate	△	?	Y	*	?	Y	*	*	?	N	N	?	?	?	Y	Y	Y	N	Y	Y	◆	Y	
Haloperidol	△	Y	Y	?	*	Y	Y	Y	Y	N	N	Y	?	Y	Y	Y	?	N	N	Y	◆	Y	
Hydromorphone	△	N	*	Y	Y	*	N	Y	Y	Y	N	*	Y	Y	Y	*	?	N	N	Y	◆	Y	
Hyoscine butylbromide	△	N	?	*	Y	N	*	*	?	?	N	N	Y	Y	Y	Y	Y	N	N	Y	◆	Y	
Hyoscine hydrobromide	△	?	Y	*	Y	Y	*	*	?	Y	N	Y	Y	Y	Y	Y	?	N	?	Y	◆	Y	
Ketamine	△	?	Y	?	Y	Y	?	?	*	N	?	N	?	Y	Y	Y	?	N	N	Y	◆	Y	
Ketorolac	△	N	Y	N	N	Y	?	Y	N	*	N	Y	N	N	N	N	?	N	Y	Y	◆	N	
Lignocaine	△	N	N	N	N	N	N	N	?	N	*	N	N	Y	N	?	N	N	N	Y	◆	Y	
Methadone	△	?	*	?	Y	*	N	Y	N	Y	N	*	Y	Y	Y	*	N	N	N	Y	◆	Y	
Methotrimeprazine	△	Y	Y	?	?	Y	Y	Y	?	N	N	Y	*	Y	Y	Y	Y	N	N	Y	◆	Y	
Metoclopramide	△	Y	Y	?	Y	Y	Y	Y	Y	N	Y	Y	Y	*	Y	Y	Y	N	N	Y	◆	Y	
Midazolam	△	?	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	*	Y	Y	N	?	Y	◆	Y	
Morphine	△	Y	*	Y	Y	*	Y	Y	Y	N	?	*	Y	Y	Y	*	Y	N	N	Y	◆	Y	
Octreotide	△	?	Y	Y	?	?	Y	?	?	?	N	N	Y	Y	Y	Y	*	N	N	Y	◆	Y	
Phenobarbitone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*	N	N	◆	Y
Ranitidine	△	?	?	Y	N	N	N	?	N	Y	N	N	N	N	?	N	N	N	*	Y	◆	N	
Sodium chloride 0.9%	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	*	◆	*	
Sufentanil	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	*	◆
Water for injection	△	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	*	◆	*	

**KEY TO COMPATIBILITY SYMBOLS**

Y	Acceptable combination, literature contains reports of compatibility.
N	Do NOT mix, incompatible or requires administration alone for other reasons.
*	Same or similar medication, no benefit in mixing.
?	Insufficient data, do NOT mix.
△	Although some compatibility data exists, do NOT give clonazepam by syringe driver; it adsorbs onto PVC and is prone to precipitation.
◆	Although some compatibility data exists, sufentanil only to be used with specialist advice.

**DILUENT NOTES**

- Solutions containing cyclizine should only be made up with water.
- Although methotrimeprazine may be diluted with water, sodium chloride is the preferred diluent.

## DRUG INTERACTIONS

The interaction sections of the drug monographs include only those interactions which may occur between drugs routinely used in Palliative Care. It is important to note that other interactions may need to be taken into account when patients are receiving drugs not included in this formulary.

Prescribers and those caring for patients are advised to be alert to, and seek further advice on, interactions wherever necessary. Most of the commonly encountered drug interactions fall into one of two categories:

- Cytochrome P450 system interactions
- Pharmacodynamic interactions

### Cytochrome P450 system interactions

The Cytochrome P450 enzyme system is involved in the metabolism of many drugs and interactions mediated by this system account for many of those that have potentially serious outcomes.

The potential for Cytochrome P450 system interactions is due to the fact that the system may be induced (leading to more rapid metabolism of drug substrates and therefore reduced effect) or inhibited (leading to slower metabolism of drug substrates and therefore increased effect). There are a large number of commonly used drugs that are inducers or inhibitors of the Cytochrome P450 system and many of these are used in palliative care.

<b>Examples of drugs which are Cytochrome P450 inducers and inhibitors that may cause clinically significant drug interactions</b>	
<b>Inducers</b>	<b>Inhibitors</b>
Carbamazepine Dexamethasone Barbiturates e.g. phenobarbitone Phenytoin Rifampicin St Johns Wort ( <i>Hypericum</i> ) Tobacco smoke	Cimetidine Diltiazem Esomeprazole Fluconazole Fluoxetine Grapefruit juice Haloperidol Ketoconazole Metronidazole Macrolide antibiotics e.g. erythromycin Miconazole Omeprazole Paroxetine Protease inhibitors e.g. ritonavir Quinidine Valproate sodium Verapamil

Although a large number of drugs are metabolised by the Cytochrome P450 system, the therapeutic window for some drugs is sufficiently wide such that changes in plasma levels due to induction or inhibition of the Cytochrome P450 system may not give rise to toxic or sub-therapeutic effects. There are, however, a number of drugs where the therapeutic window is narrow and it is these that are most prone to clinically significant interactions.

<b>Examples of drugs (“substrates”) with a narrow therapeutic range that are metabolised by the Cytochrome P450 system</b>
--

Benzodiazepines e.g. diazepam, midazolam Carbamazepine Ciclosporin Oral anticoagulants e.g. warfarin Phenytoin Phenobarbitone Pimozide Theophylline Tricyclic antidepressants e.g. amitriptyline, nortriptyline
---

The Cytochrome P450 system comprises a number of individual isoenzymes and some drugs are substrates for a specific isoenzyme, others for a range of isoenzymes. Similarly, some inducers and inhibitors may have effects on one or more isoenzymes. The isoenzymes have been classified and allocated a number to aid description, for example CYP2C9 or CYP3A4. Therefore for Drug A to interact with Drug B; Drug A (which could be an inhibitor or inducer) needs to have an effect on the same isoenzyme(s) that are involved in metabolism of Drug B. For example, if Drug A only induces or inhibits CYP2C9 and Drug B is only metabolised by CYP3A4, an interaction is unlikely to occur.

In day to day clinical practice, it is not necessary to consider the various Cytochrome P450 isoenzymes, consequently details of the isoenzymes involved in individual interactions have been omitted from the drug monographs.

### **Pharmacodynamic interactions**

These interactions occur where two drugs may have additive or opposing effects. Commonly encountered examples with additive effects include:

- Drugs with central nervous system (CNS) depressant effects, when given together may lead to profound sedation
  - For example midazolam and haloperidol
- Drugs with anticholinergic effects, when given together may increase the risk of adverse events such as urinary retention
  - For example amitriptyline and hyoscine butylbromide
- Drugs with respiratory depressant effects, when given together increase the risk of respiratory arrest
  - For example morphine and diazepam
- Drugs with effects to prolong the QT interval, when given together increase the risk of ventricular arrhythmias
  - For example methadone and domperidone
- Drugs with serotonergic effects, when given together increase the risk of serotonin syndrome
  - For example tramadol and citalopram
- Drugs which cause gastro-intestinal irritation and/or prolong clotting time, when given together increase the risk of gastric bleeding

- For example diclofenac and fluoxetine

In some cases the use of a combination of drugs, with for example sedative effects (such as morphine and haloperidol), may be intentional and not undesirable. However, in some cases the additive effects may be due to secondary properties of the drugs e.g. the anticholinergic effects of tricyclic antidepressants, and these may be less predictable and subsequently more problematic.

In other cases there is the potential for drugs given concomitantly to oppose each other. For example the effects of salbutamol given for wheeze would be opposed by propranolol given for angina, as these are agonists and antagonists of the same receptors.

## “OFF-LABEL” PRESCRIBING

In Palliative Care, a high proportion of prescribing is for licensed medicinal products given “off-label” (or outside of license). This may involve use:

- for unlicensed clinical indications
- via an unlicensed route
- at a dose beyond the licensed maximum
- in patient groups excluded from the license e.g. elderly, hepatic impairment

In addition to these scenarios there are two other situations where unlicensed prescribing occurs:

- use of a drug which although available in a licensed formulation, is administered as a formulation which is not licensed e.g. a special or extemporaneous product.
- use of a drug which is not available in any form as a licensed product e.g. an experimental drug or one only available as a licensed product elsewhere in the world.

A number of factors should be taken into account when considering unlicensed prescribing:

Drug	How well known is the drug to the prescriber and in the medical community generally?
Product	Is the product licensed for the indication, at the dose and by the route being considered?
Evidence	What data is available to support this use; is it supported by robust trials, peer opinion, anecdotal evidence or no data at all?
Patient	How serious is the condition or how much is it affecting the patients quality of life?

The balance of these factors will vary widely from scenario to scenario and each must be judged on a case by case basis. A hierarchy of reasonableness has been compiled in the UK Palliative Care Formulary (PCF3), reference to which prescribers may find useful.

The Australian Medical Association (AMA) position is that: ‘Off-label prescribing’ is the prescription of a registered medicine for a use that is not included in the product information. Off-label prescribing may be clinically appropriate, but is associated with a number of clinical, ethical and medico-legal issues. The AMA supports greater research and the application of evidence-based principles to provide guidance for medical practitioners when making decisions to prescribe off-label or unlicensed medicines.

It is important to recognise the impact that unlicensed prescribing may have on patients and the carers. Consumer medical information (CMI) leaflets only contain information on the licensed indications for medicines and without explanation (and ideally formal consent) this can give rise to problems. In some cases patients may think they have been given the wrong medicine or worry about side effects that only occur when the medicine is used for a different condition at a higher dose. In these situations patients may not start to take their medicines or may stop them prematurely, with the consequence that they may fail to see an improvement in their symptoms.

Explaining the use of medicines outside of license is not always easy and a number of centres have consequently produced an information leaflet for Palliative Care patients which provides generic information about this subject. An example which is considered appropriate for use in Tasmania is produced in Appendix I.

## **Appendix I.**

### **Use of Medicines in Palliative Care**

This leaflet provides important information about one way that medicines are often used in the Palliative Care service, please read it carefully and keep it for future reference.

#### **What is a licensed medicine?**

The companies who make medicines must apply to the government for a licence if they want to sell their medicine in Australia. The companies carry out large studies called clinical trials to prove to the government's Therapeutic Goods Administration (TGA) agency that the medicine works for the illness it is intended to treat, that it does not have too many side effects, and has been made to a high standard.

The license describes the way the medicine should be used and covers subjects such as the medical conditions it is for, the dose that should be used, and the type of patient it is suitable for. When you read the Consumer Medicine Information (CMI) provided with medicines, the information you are given only relates to the licensed uses of the medicine.

#### **What is an outside of license medicine?**

Although a medicine's license will usually cover its most common uses, doctors sometimes find using the medicine in a different way is useful.

When the way a medicine is used is different to that described in the license, it is called "outside of license" or "off-label". In Palliative Care it is quite common for some medicines to be prescribed outside of their license.

#### **Why are medicines used outside of license?**

Every patient and their condition are different. Although there are thousands of different licensed medicines, your doctor may consider that using a medicine outside of license is the best answer to provide you with relief of your symptoms.

There are a number of reasons as to why medicines are used outside of their licences:

- The clinical trials carried out by the drug companies will only have tested the drug on particular illnesses. However, doctors have found that the medicine works well in other illnesses and expert groups have made suggestions about how the drug could be used in these illnesses. The licence cannot be used to cover the new illnesses without further clinical trials being carried out.
- Sometimes people need doses that are different from or higher than the doses that are tested in clinical trials.
- Sometimes the medicine needs to be given in a different way to that described in the license. For example if someone has swallowing difficulties it may be better to give the medicine by injection under the skin (sub-cutaneously) rather than by injection into a vein or as a tablet.

- Most clinical trials are carried out in adults aged 18-65 and therefore the licence only covers people in that age range, but doctors may find that the medicine is useful in younger or older people.

**Should I be worried about taking medicines outside of license?**

No. Your doctor will have carefully considered the best option for you and will have a good knowledge of using the medicine in this way. Your doctor can explain to you why they feel this is the best option for you.

**Remember**

When a medicine has been prescribed outside of license not all the information in the CMI may apply to your circumstances. If you are worried about taking this medicine please do not hesitate to discuss any concerns with your doctor, nurse or pharmacist and they will be able to support and advise you.