

# AUSTRALIAN PRODUCT INFORMATION, PAINSTOP NIGHT-TIME PAIN RELIEVER (PARACETAMOL 120MG IN 5ML, CODEINE PHOSPHATE HEMIHYDRATE 5MG IN 5ML AND PROMETHAZINE HYDROCHLORIDE 6.5MG IN 5ML)

## 1. NAME OF THE MEDICINE

Paracetamol, codeine phosphate hemihydrate and promethazine hydrochloride.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Painstop Night-Time Pain Reliever contains the following active ingredients: Paracetamol 24 mg in 1mL, codeine phosphate hemihydrate 1 mg in 1mL and promethazine hydrochloride 1.3 mg in 1mL; and the following inactive ingredients (excipients) with known effect: saccharin sodium, disodium edetate, sodium metabisulfite and sucrose. For the full list of excipients see Section 6.1. 'List of excipients'.

## 3. PHARMACEUTICAL FORM

Painstop Night-Time Pain Reliever is a maroon coloured liquid for oral use (dosage form: 'oral liquid'). It is presented in 100mL & 200mL amber glass bottles with a child resistant cap.

## 4. CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

For the temporary relief of acute moderate pain when paracetamol alone is not sufficient and sedation is considered beneficial in patients over the age of 12 years (see also 4.3 CONTRAINDICATIONS and 4.4 Special Precautions and Warnings for Use – Paediatric Use).

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years and older: 20 to 35 mL to be taken as a single bed-time dose when needed to relieve pain and aid sleep.

Do not give more than the recommended dose.

Do not use for more than 24 hours except on medical advice. Painstop Night-Time Pain Reliever

Is contraindicated for use in children:

- Younger than 12 years.
- Aged between 12 – 18 years in whom respiratory function might be compromised, including post-tonsillectomy and / or adenoidectomy for obstructive sleep apnoea (see 4.3 and 4.4 – Paediatric Use).

#### 4.3 CONTRAINDICATIONS

Painstop Night-Time Pain Reliever Is contraindicated for use in patients who are:

- CYP2D6 ultra-rapid metabolisers (see 4.4 Special Precautions and Warnings for Use – CYP2D6 metabolism).
- Younger than 12 years (see 4.4 Special Precautions and Warnings for Use – Paediatric Use).
- Aged between 12 and 18 years in whom respiratory function might be compromised, including post tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, due to an increased risk of developing serious and life- threatening adverse reactions (see 4.4 Special Precautions and Warnings for Use – Paediatric Use).
- Breastfeeding (see 4.4 Special Precautions and Warnings for Use – Use in Lactation).
- With acute respiratory depression.
- With chronic constipation.
- With active alcoholism.
- With diarrhoea caused by pseudomembranous colitis or poisoning (until the causative organism or toxin has been eliminated from the gastrointestinal tract, since codeine may slow down the elimination, thereby prolonging the diarrhoea)
- With narrow-angle glaucoma.
- With stenosing peptic ulcer.
- With symptomatic prostatic hypertrophy.
- With bladder neck obstruction.
- With pyloroduodenal obstruction.

Painstop Night-Time Pain Reliever should not be used in patients taking monoamine oxidase inhibitors (MAOIs).

Refer to 4.5 'Interactions with other medicines and other forms of interaction' for additional information.

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

##### CYP2D6 metabolism

Painstop Night-Time Pain Reliever is contraindicated for use in patients who are CYP2D6 ultra-rapid metabolisers.

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels. General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Children are particularly susceptible due to their immature airway anatomy. Deaths have been reported in children with rapid metabolism who were given codeine for analgesia post adenotonsillectomy. Morphine can also be ingested by infants through breast milk, causing risk of respiratory depression to infants of rapid metaboliser mothers who take codeine.

The prevalence of codeine ultra-rapid metabolism by CYP2D6 in children is not known but is assumed to be similar to that reported in adults. The prevalence of ultra-rapid metabolisers is estimated to be 1% in those of Chinese, Japanese and Hispanic descent, 3% in African Americans and 1%-10% in Caucasians. The highest prevalence (16%-28%) occurs in North African, Ethiopian and Arab populations.

(See also sections 4.4 Special Precautions and Warnings for Use – Paediatric Use and 4.6 Use in Fertility, pregnancy and lactation - Use in Lactation.)

##### *Paediatric Use*

Painstop Night-Time Pain Reliever is contraindicated for use in children:

- Younger than 12 years.
- Aged between 12 and 18 years in whom respiratory function might be compromised, including post tonsillectomy and/or adenoidectomy for obstructive sleep apnoea. Respiratory depression and death have occurred in some children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine due to a CYP2D6 polymorphism.

(See also 4.4 Special Precautions and Warnings for Use – CYP2D6 metabolism).

#### *Additional precautions*

Painstop Night-Time Pain Reliever should be used with caution in patients:

- With decreased respiratory reserve e.g., asthma or COPD.
- With pre-existing respiratory depression. Painstop Night-Time Pain Reliever is contraindicated for use in patients with acute respiratory depression (see section 4.3 CONTRAINDICATIONS).
- Who have a history of drug abuse.
- Who are taking other respiratory depressants or sedatives, including alcohol.
- Who have had recent gastrointestinal tract surgery.
- With raised intracranial pressure or head injury.
- With prostatic hypertrophy.
- With hepatic or renal impairment.
- With hypertension.
- With hypothyroidism.
- With epilepsy with diabetes mellitus.

Codeine may obscure the diagnosis or the course of gastrointestinal diseases. Prolonged use of codeine may produce physical and psychological dependence.

Refer to 4.5 'Interactions with other medicines and other forms of interaction' for additional information.

#### *Use in hepatic impairment*

Painstop Night-Time Pain Reliever should be used with caution in patients with impaired hepatic function.

#### *Use in renal impairment*

Painstop Night-Time Pain Reliever should be used with caution in patients with impaired renal function.

### *Paediatric Use*

Children may experience paradoxical excitation with promethazine hydrochloride. Painstop Night-Time Pain Reliever is contraindicated for use in children:

- Younger than 12 years.
- Aged between 12 – 18 years in whom respiratory function might be compromised, including post-tonsillectomy and / or adenoidectomy for obstructive sleep apnoea. Respiratory depression and death have occurred in some children who received codeine following tonsillectomy and / adenoidectomy and had evidence of being ultra-rapid metabolisers of codeine due to a CYP2D6 polymorphism.

See also 4.4 Special Precautions and Warnings for Use – CYP2D6 metabolism.

### *Use in the elderly*

The elderly are more likely to have age related renal impairment and may be more susceptible to the respiratory depressant effects of codeine.

They may experience paradoxical excitation with promethazine hydrochloride and are more likely to have central nervous system (CNS) depressive side-effects, including confusion.

### *Effects on laboratory tests*

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

The following interactions with codeine have been noted:

- CNS depressants – concomitant use with central nervous system depressants. (e.g. barbiturates, chloral hydrate, sedatives, alcohol and centrally acting muscle relaxants) can cause additive CNS depression.
- Anticholinergics – concurrent use of codeine with anticholinergic agents may increase the risk of severe constipation and/or urinary retention.
- Antihypertensives – hypotensive effects may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.
- Antiperistaltic antidiarrhoeals (e.g. kaolin, pectin and loperamide) – concurrent use with codeine may increase the risk of severe constipation.
- Metoclopramide – codeine may antagonise the effects of metoclopramide on

gastrointestinal activity.

- Monoamine oxidase inhibitors (MAOIs) – concurrent administration or use within 14 days of ceasing MAOIs may enhance the potential respiratory depressant effects of codeine.
- Opioid analgesics – concurrent use of codeine and other opioid receptor antagonists is usually inappropriate as additive CNS depression, respiratory depression and hypotensive effects may occur.
- Substances that inhibit CYP2D6 such as quinidine, phenothiazines and antipsychotic agents can interfere with the metabolism of codeine to morphine, reducing the analgesic effect of codeine.
- Tranquillisers, sedatives and hypnotics – codeine may potentiate the effects of these preparations.

The following interactions with paracetamol have been noted:

- Anticoagulant drugs (warfarin) - dosage may require reduction if paracetamol and anticoagulants are taken for a prolonged period of time.
- Paracetamol absorption is increased by substances that increase gastric emptying, e.g. metoclopramide.
- Paracetamol absorption is decreased by substances that decrease gastric emptying, e.g. propantheline, antidepressants with anticholinergic properties, and narcotic analgesics.
- Paracetamol may increase chloramphenicol concentrations.
- The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes such as alcohol and anticonvulsant agents.
- Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.
- Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

The following interactions with promethazine hydrochloride have been noted:

- Central nervous system (CNS) depressants (alcohol, sedatives, opioid analgesics, hypnotics) – may cause an increase in sedation effects.
- Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) – may prolong and intensify the anticholinergic and CNS depressive effects.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### *Effects on fertility*

No data available

### *Use in pregnancy*

Painstop Night-Time Pain Reliever is defined as Category C.

Promethazine, owing to its pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

When promethazine has been given in high doses during late pregnancy, promethazine has caused prolonged neurological disturbances in the infant.

Promethazine should be used in pregnancy only if the potential benefits to the patient are weighed against the possible risk to the foetus.

### *Use in lactation*

Painstop Night-Time Pain Reliever is contraindicated during breastfeeding (see also 4.4 Special Precautions and Warnings for Use – CYP2D6 metabolism) due to risk of respiratory depression in the infant.

Analgesic doses excreted in breast milk are generally low. However, infants of breastfeeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultrarapid metaboliser of codeine. Codeine is excreted into human breast milk. Codeine is partially metabolised by cytochrome P4502D6 (CYP2D6) into morphine, which is excreted into breast milk. If nursing mothers are CYP2D6 ultra-rapid metabolisers, higher levels of morphine may be present in their breast milk. This may result in symptoms of opioid toxicity in both mother and the breastfed infant. Life-threatening adverse events or neonatal death may occur even at therapeutic doses (see also 4.4 Special Precautions and Warnings for Use – CYP2D6 metabolism).

Therefore, Painstop Night-Time Pain Reliever is contraindicated for use during breastfeeding. However, in circumstances where a breastfeeding mother requires codeine therapy, breastfeeding should be suspended and alternative arrangements should be made for feeding the infant for any period during codeine treatment.'

Breastfeeding mothers should be told how to recognise signs of high morphine levels in themselves and their babies. For example, in a mother, symptoms include extreme sleepiness and trouble caring for the baby. In the baby, symptoms include signs of increased sleepiness (more than usual), difficulty breastfeeding, breathing difficulties, or limpness. Medical advice should be sought immediately.

#### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Painstop Night-Time Pain Reliever may cause drowsiness and may increase the effects of alcohol. Drowsiness may continue the following day. Those affected should not drive or operate machinery; alcohol should be avoided.

#### 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Side effects of paracetamol are rare and usually mild, although haematological reactions have been reported. Skin rashes and hypersensitivity reactions occur occasionally. Overdosage with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

The most common adverse effects associated with codeine are nausea, vomiting, drowsiness, dizziness and constipation. Other side effects are rare. These include: cough suppression, respiratory depression, euphoria, dysphoria, skin rashes, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions. Prolonged use of codeine may produce physical and psychological dependence.

Central nervous system (CNS) depressive effects of promethazine hydrochloride include sedation and impaired performance (impaired driving performance, poor work performance, incoordination, reduced motor skills, and impaired information processing). Performance may be impaired in the absence of sedation and may persist the morning after a night-time dose.

CNS stimulatory effects of promethazine hydrochloride may include anxiety, hallucinations, appetite stimulation, muscle dyskinesias and activation of epileptogenic foci.

High doses of promethazine may cause nervousness, tremor, insomnia, agitation, and irritability.

Anticholinergic effects of promethazine include dryness of the eyes, mouth and nose, blurred vision, urinary hesitancy and retention, constipation and tachycardia.



Children and the elderly are more likely to experience adverse effects than other age groups.

Each 5mL of Painstop Night-Time Pain Reliever contains 880mg of Sorbitol. Products containing sorbitol may have a laxative effect or cause diarrhoea.

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

#### 4.9 OVERDOSE

For information on the management of overdose, contact the poison information centre on 13 11 26 (Australia); in New Zealand call 0800 764 766.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

##### *Mechanism of action*

Paracetamol is a p-aminophenol derivative that exhibits analgesic and antipyretic activity. It does not possess anti-inflammatory activity. Paracetamol is thought to produce analgesia through a central inhibition of prostaglandin synthesis.

Codeine acts centrally. It has an analgesic effect, which is thought to be due mainly to its partial metabolic conversion to morphine. Codeine has about one-sixth the analgesic activity of morphine.

Promethazine hydrochloride competes with histamine at central and peripheral histamine<sub>1</sub>-receptor sites, preventing the histamine-receptor interaction and subsequent mediator release. Promethazine hydrochloride is a highly lipophilic molecule that readily crosses the blood-brain barrier. Promethazine hydrochloride is highly selective for histamine<sub>1</sub>-receptors but has little effect on histamine<sub>2</sub> or histamine<sub>3</sub> receptors. Promethazine hydrochloride also activates 5-hydroxytryptamine (serotonin) and  $\alpha$ -adrenergic receptors and blocks cholinergic receptors.

##### *Clinical trials*

No data available

## 5.2 PHARMACOKINETIC PROPERTIES

### *Absorption*

Codeine and its salts are well absorbed from the gastrointestinal tract: peak plasma- codeine concentrations occur at about one hour after ingestion of codeine phosphate.

Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral administration. The elimination half-life varies from about 1 to 3 hours.

Promethazine hydrochloride is well absorbed after oral administration. Peak plasma concentrations have been observed 2 to 3 hours after administration.

### *Distribution*

Codeine crosses the placenta and is distributed into breast milk.

Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses.

Promethazine crosses the blood-brain barrier and the placenta, and is distributed in the breast milk.

### *Metabolism*

Codeine is metabolised by O- and N-demethylation in the liver (via the cytochrome P450 system) to morphine (about ten per cent of a codeine dose is demethylated to morphine), norcodeine and other metabolites including normorphine and hydrocodone. The plasma half-life of codeine has been reported to be between 3 and 4 hours after oral administration.

About 8% of patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite.

Paracetamol is metabolised extensively in the liver and excreted in the urine mainly as inactive glucuronide and sulfate conjugates. Less than 5% is excreted unchanged. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione, however, it can accumulate following paracetamol overdose (more than 150mg/kg or 10g total paracetamol

ingested) and if left untreated can cause irreversible liver damage.

Paracetamol is metabolised differently by premature infants, newborns, infants and young children compared to adults, the sulfate conjugate being predominant.

Promethazine has low systemic bioavailability after oral administration due to first-pass metabolism in the liver. Values ranging from 76 to 93% have been reported for plasma- protein binding. Promethazine undergoes extensive metabolism, predominantly to promethazine sulfoxide, and also to N-desmethylpromethazine.

#### *Excretion*

Codeine and its metabolites are excreted almost entirely by the kidney, mainly as conjugates with glucuronic acid. Approximately 3% to 16% of a dose is eliminated unchanged in the urine.

Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol.

Promethazine is excreted slowly via the urine and bile, chiefly as metabolites. Elimination half-lives of 5 to 14 hours have been reported.

### 5.3 PRECLINICAL SAFETY DATA

No data available.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Saccharin sodium, disodium edetate, sodium metabisulfite, sucrose, propylene glycol, sorbitol (880mg per 5mL), imitation toffee flavour, imitation strawberry flavour, brilliant blue CI 42090, amaranth CI 16185 and purified water. Each 5mL of oral liquid also contains 880mg of Sorbitol.

### 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

The duration of shelf life of Painstop Night-Time Pain Reliever is 24 months.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Painstop Night-Time Pain Reliever should be stored below 25 degrees Celsius, do not refrigerate.

### 6.5 NATURE AND CONTENTS OF CONTAINER

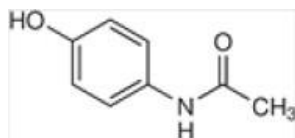
Painstop Night-Time Pain Reliever is presented in 100mL & 200mL amber PET bottles with a child resistant cap.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

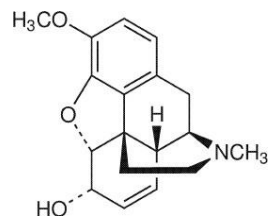
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

### 6.7 PHYSICOCHEMICAL PROPERTIES

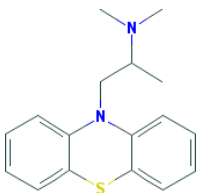
*Chemical structure of paracetamol*



*Chemical structure of codeine*



### Chemical structure of promethazine hydrochloride



### CAS numbers

Codeine phosphate:	52-28-8
Paracetamol:	103-90-2
Promethazine hydrochloride:	58-33-3

## 7. MEDICINES SCHEDULE (POISONS STANDARD)

Painstop Night-Time Pain Reliever is included in schedule 4 ('Prescription Only Medicine').

## 8. SPONSOR

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## 9. DATE OF FIRST APPROVAL

Painstop Night-Time Pain Reliever was first included in the Australian Register of Therapeutic Goods on 15 October 1991

## 10. DATE OF REVISION

26 March 2018

*Summary table of changes*

Section changed	Summary of new information
All sections	Format changed to meet TGA requirements from 1 January 2018
4.1 Therapeutic indications	Wording of the indications amended to more closely relate to use in medical practice.
4.3 Contraindications	Additional information included in relation to use in children between 12 and 18 years
4.4 Special warnings and precautions for use	<p>CYP2D6 metabolism: Additional information included in relation to patients who are ultra-rapid metabolisers of codeine.</p> <p>Paediatric use: Additional information included in relation to possible links between codeine use and respiratory depression and death following tonsillectomy and / or adenoidectomy in children with evidence of being ultra-rapid metabolisers of codeine due to a CYP2D6 polymorphism.</p>
4.6 Use in lactation	Additional information included in relation to codeine being contraindicated for use during lactation
7	Update to poisons scheduling from 1 February 2018
8	Update of sponsor's address details