AUSTRALIAN PRODUCT INFORMATION, PAINSTOP DAY-TIME PAIN RELIEVER (PARACETAMOL 120MG IN 5ML AND CODEINE PHOSPHATE HEMIHYDRATE 5MG IN 5ML)

1. NAME OF THE MEDICINE

Paracetamol and codeine phosphate hemihydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Painstop Day-Time Pain Reliever contains the following active ingredients: Paracetamol 24 mg in 1mL and codeine phosphate hemihydrate 1 mg in 1mL; and the following inactive ingredients (excipients) with known effect: methyl hydroxybenzoate, propyl hydroxybenzoate and saccharin sodium. For the full list of excipients see Section 6.1. 'List of excipients'.

3. PHARMACEUTICAL FORM

Painstop Day-Time Pain Reliever is a clear colourless solution with a tutti fruity flavour for oral use (dosage form: 'oral liquid'). It is presented in 100mL & 200mL amber PET 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 in patients over the age of 12 years (see also 4.3 CONTRAINDICATIONS and Paediatric use).

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children 12 years and over: 20 mL to 35 mL orally every 6 hours as needed.

4.3 CONTRAINDICATIONS

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

- CYP2D6 ultra-rapid metabolisers (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Younger than 12 years (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS 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 WARNINGS AND PRECAUTIONS FOR USE - Paediatric Use).

- Breastfeeding (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in lactation).
- With known hypersensitivity or idiosyncratic reaction to paracetamol, codeine or any of the other ingredients in the product.
- With acute respiratory depression.
- With chronic constipation.
- During labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate.
- 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).

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 Day-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.

(Refer to 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in lactation and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use)

Paediatric use

Painstop Day-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 WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 metabolism)

Additional precautions

Codeine should be used with caution in patients:

- With decreased respiratory reserve e.g. asthma or COPD. Painstop Day-Time Pain Reliever is contraindicated for use in patients with acute respiratory depression (see 4.3 CONTRAINDICATIONS).
- With pre-existing respiratory depression.
- 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.

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

Use in hepatic impairment

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

Use in renal impairment

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

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.

Effect 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy

Category A: Codeine and paracetamol have been taken by a large number of pregnant women and women of child bearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Opioid analgesics may cause respiratory depression in the newborn infant. Prolonged high-dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate. Painstop Day-Time Pain Reliever is contraindicated for use during labour when delivery of a premature infant is anticipated as it may produce codeine withdrawal symptoms in the neonate (see CONTRAINDICATIONS).

Use in lactation

Painstop Day-Time Pain Reliever is contraindicated during breastfeeding (see also 4.4 SPECIAL WARNINGS AND PRECAUTIONS 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 WARNINGS AND PRECAUTIONS FOR USE – CYP2D6 metabolism).

Therefore, Painstop Day-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

Codeine may cause drowsiness. Those affected should not drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse 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 effects 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.

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 Poisons Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

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.

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.

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.

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 overdosage (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.

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.

5.3 PRECLINICAL SAFETY DATA

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Macrogol, glycerol, sodium chloride, citric acid monohydrate, sodium citrate, methyl hydroxybenzoate, propyl hydroxybenzoate, saccharin sodium, xanthan gum, menthol, tutti frutti flavour and water purified.

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 Day-Time Pain Reliever is 24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

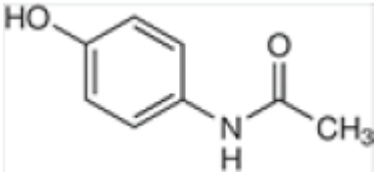
Painstop Day-Time Pain Reliever is presented in 100mL & 200mL amber PET bottles with a child resistant cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

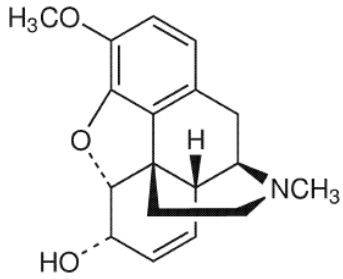
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure of paracetamol



Chemical structure of codeine



CAS numbers

Codeine phosphate: 52-28-8
Paracetamol: 103-90-2

7. MEDICINES SCHEDULE (POISONS STANDARD)

Painstop Day-Time Pain Reliever is included in schedule 4 (‘Prescription Only Medicine’).

8. SPONSOR

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9. DATE OF FIRST APPROVAL

Painstop Day-Time Pain Reliever was first included in the Australian Register of Therapeutic Goods (ARTG) on 26 September 2006.

10. DATE OF REVISION

7 March 2018

Summary table of changes

Section changed	***Summary of new information***
All sections	Format changed to meet new TGA requirements 1 January 2018