

# CORE PRODUCT INFORMATION for PARACETAMOL/CODEINE COMBINATION ANALGESIC

## Product description

*This section should include:*

- *a description of the dosage form;*
- *a list of the active ingredients, using Australian Approved Names (AANs) and expressed quantitatively; and*
- *a list of the excipients, using Australian Approved Names (AANs) and expressed qualitatively*

## Pharmacology

### Pharmacokinetics:

**Paracetamol:** Paracetamol is readily absorbed from the gastrointestinal tract with peak plasma concentrations occurring about 10 to 60 minutes after oral administration. Paracetamol is distributed into most body tissues. Plasma protein binding is negligible at usual therapeutic doses but increases with increasing doses. The elimination half-life varies from about 1 to 3 hours.

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.

**Codeine:** 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.

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. 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.

About 8% of people metabolise drugs poorly via CYP2D6, and are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite, morphine.

The plasma half-life of codeine has been reported to be between 3 and 4 hours after oral administration.

#### **Pharmacodynamics/Mechanism of action:**

**Paracetamol:** 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:** 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.

Systematic reviews<sup>1,2,3</sup> comparing paracetamol-codeine combinations versus paracetamol alone concluded that in single-dose studies addition of codeine to paracetamol produced a comparatively small but statistically significant increase in analgesic effect; however, there was an increased incidence of adverse effects with the combination.

1. de Craen AJM, *et al.* Analgesic efficacy and safety of paracetamol-codeine combinations versus paracetamol alone: a systematic review. *BMJ* 1996; 313: 321–5. [PubMed](#)
2. Moore A, *et al.* Single dose paracetamol (acetaminophen), with and without codeine, for postoperative pain. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1998. [PubMed](#)
3. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD001547. DOI:10.1002/14651858.CD001547.pub2.

## **Indications**

*This section must contain the indications of the product as specified in the ARTG. If the indications are not specified in the ARTG (e.g. for a non-validated grandfathered product), the indications must be as specified on an approved product label.*

*It should be noted that, if labels of grandfather products have not been approved by the TGA or the ARTG indications have not been validated through OPAL, then the PI will require evaluation.*

## **Contraindications**

[*Product name*] is contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to paracetamol, codeine or other opiates (or any of the other ingredients in the product).

It is also contraindicated for use in patients:

- 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 'Interactions with other medicines' for additional information.

## **Precautions**

[*Product name*] should be used with caution in patients with:

- impaired hepatic function
- impaired renal function
- decreased respiratory reserve e.g. asthma or chronic obstructive pulmonary disease (COPD)
- pre-existing respiratory depression
- raised intracranial pressure or head injury
- prostatic hypertrophy
- hypotension
- hypothyroidism

It should also be used with caution in patients who:

- have a history of drug abuse
- are taking other respiratory depressants or sedatives, including alcohol
- have had recent gastrointestinal tract surgery

Codeine may obscure the diagnosis or the course of gastrointestinal diseases.

Prolonged use of codeine may produce physical and psychological dependence.

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

Refer to 'Interactions with other medicines' for additional information.

## **Use in pregnancy**

Category A: Both paracetamol and codeine have been taken by a large number of pregnant women and women of childbearing 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.

## **Use in lactation**

Paracetamol and codeine both appear in breast milk in low concentrations. Maternal ingestion of paracetamol in recommended doses does not appear to present a risk to breastfed infants. However, codeine may cause respiratory depression in newborn infants.

[*Product name*] is therefore not recommended for breastfeeding mothers unless the potential benefits to the patient outweigh the possible risk to the infant.

### **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.

### **Interaction with other medicines**

The following interactions 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
- Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.
- CNS depressants – concomitant use of codeine 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 substances.

## **Adverse reactions**

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 include: cough suppression, respiratory depression, euphoria, dysphoria, skin rashes, histamine release (hypotension, flushing of the face, tachycardia, breathlessness) and other allergic reactions.

## **Dosage**

*This section must contain the current dosage instructions of the registered product, as specified on the product label. Non-validated grandfathered products will have to undergo full evaluation by the TGA.*

## **Overdosage**

If an overdose is taken or suspected, immediately contact the Poisons Information Centre (in Australia, call 131 126; in New Zealand call 0800 764 766) for advice, or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage with paracetamol.

## **Presentation**

*Information should be included on:*

- *the presentation, including dosage form and pack sizes;*
- *identifying details (eg. colour, shape, identifying markings);*
- *poisons schedule details; and*
- *name and address of the sponsor*

*Include the date of approval.*