

# Data Sheet

## ParaCode

*Paracetamol 500 mg and Codeine Phosphate 8 mg Tablets*

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## Presentation

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White to off-white round tablets with beveled edges, plain on one side and a break line on the other side.

Each ParaCode tablet contains paracetamol 500 mg and codeine phosphate 8 mg. Other ingredients include magnesium stearate, maize starch, povidone and starch.

ParaCode tablets DO NOT contain gluten, lactose or sucrose.

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## Uses

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### **Actions**

Analgesic and antipyretic.

Paracetamol's analgesic mechanism of action has not been fully elucidated but may involve blocking impulse generation at the bradykinin-sensitive chemoreceptors, that evoke pain.

The antipyretic effect of paracetamol rises from its ability to block the action of prostaglandin synthetase and so prevent the synthesis of prostaglandins in response to the pyrogen stimulus in the region of the anterior hypothalamus.

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.

There is evidence to suggest that a combination of paracetamol with codeine is superior in analgesic action to either drug administered alone.

### **Pharmacokinetics**

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 30 to 120 minutes after administration. Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg.

Paracetamol can cross the placenta and is excreted in milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45-55%) or sulfate (20-30%). A minor proportion (less than 20%) is metabolised to catechol derivatives, and mercapturic acid compounds via oxidation. Paracetamol is metabolised differently by infants

and children compared to adults, the sulfate conjugate being predominant. Patients who metabolise drugs poorly via CYP2D6 (about 8%) are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite, morphine.

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1 to 4 hours. Food intake delays paracetamol absorption.

Codeine has about one-sixth of morphine's analgesic activity. It is well absorbed from the gastrointestinal tract and does not interfere with paracetamol absorption. It is metabolised in the liver to morphine and norcodeine, which with codeine, are excreted in the urine, partly as conjugates with glucuronic acid. Excretion is almost complete within 24 hours.

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## Indications

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For the temporary relief of pain and discomfort associated with:

- Headache
- Migraine Headache
- Backache
- Toothache/Dental Surgery
- Menstrual Pain
- Muscular Pain
- Neuralgia
- Cold and Flu symptoms
- Sore throat
- Arthritis

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## Contraindications

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ParaCode is contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to paracetamol, codeine, other opiates or any other ingredients in this 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.

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## Warnings and Precautions

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ParaCode 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 is excreted in breast milk but neither paracetamol nor its metabolites were detected in the urine of nursing infants after 650 mg maternal dose. Codeine does pass into breast milk so should be avoided in breastfeeding women. When ParaCode is administered to a nursing mother, alternative arrangements should be made for feeding the infant.

Analgesic doses excreted in breast milk are generally low. However, infants of breast feeding mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultrarapid metaboliser of codeine.

Breast feeding patients 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.

### ***Use in the Elderly***

The elderly are more likely to have age-related renal impairment and may be more susceptible to the respiratory effects of opioid analgesics. Dose reduction may be required.

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## Interactions

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*Salicylates and NSAIDs:* Prolonged concurrent use of paracetamol and salicylates or non-steroidal anti-inflammatory drugs may increase the risk of adverse renal effects.

*Coumarins:* Repeated high doses of paracetamol increase the risk of bleeding in patients taking warfarin and other coumarin derivatives. Monitoring of coagulation and bleeding complications is required.

*Chloramphenicol:* Paracetamol may slow down the excretion of chloramphenicol, entailing the risk of increased toxicity.

*Diflunisal:* Diflunisal may increase the plasma concentrations of paracetamol by 50%.

*Anticholinergics:* Concomitant use of codeine and anticholinergic agents may increase the risk of severe constipation and/or urinary retention. Drugs, which decrease gastric emptying, may decrease the absorption of paracetamol.

*Cholestyramine:* Cholestyramine reduces the absorption of paracetamol if given within one hour of paracetamol administration.

*Propantheline:* Decreases gastric emptying which may decrease the absorption of paracetamol.

*Rifampicin:* Concomitant use may increase the likelihood of paracetamol toxicity.

*Alcohol:* Codeine may potentiate the effects of alcohol and the likelihood of paracetamol toxicity may be increased by its concomitant use.

*Metoclopramide:* Codeine may antagonise the effects of metoclopramide on gastrointestinal motility. Paracetamol absorption is increased by drugs, which increase gastric emptying.

*Opioid analgesics:* Concurrent use of codeine and other opioid agonists is usually inappropriate as additive CNS depression, respiratory depressant and hypotensive effects may occur. Narcotic analgesics may decrease gastric emptying and therefore decrease the absorption of paracetamol.

*Tranquillisers, sedatives, hypnotics, General anaesthetics and CNS depressants:* Codeine may potentiate the effects of these drugs. Concomitant use of tranquillisers or sedatives may enhance the potential respiratory depressant effects of codeine.

*Barbiturates and antiepileptic medications:* The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol, barbiturates or anti epileptic drugs.

*Zidovudine:* When used concurrently with zidovudine, an increased tendency for neutropenia or hepatotoxicity may develop. Combination of ParaCode and zidovudine should be avoided. If chronic paracetamol and zidovudine are to be given concurrently, monitor white blood cell count and liver function tests, especially in malnourished patients.

*Antiperistaltic antidiarrhoeals (including kaolin, pectin, loperamide):* Concurrent use of these agents with codeine may increase the risk of severe constipation.

*Monoamine Oxidase Inhibitors:* Non-selective MAOI's intensify the effects of opioid drugs, which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients concurrently administered MAO inhibitors and pethidine. Codeine should not be given to patients taking non-selective MAOI's or within 10 days of stopping such treatment. As it is unknown whether there is an interaction between the selective MAOI's (Reversible Inhibitors of Monoamine Oxidase A) and codeine, caution is advised with this drug combination.

*Antihypertensives:* Hypotensive effects of antihypertensive agents may be potentiated when used concurrently with codeine and lead to orthostatic hypotension.

*Neuromuscular blocking agents:* Codeine may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

### **Effect on Laboratory Tests**

*Plasma amylase and lipase activity:* Codeine may cause increased biliary tract pressure, thus increasing plasma amylase and/or lipase concentrations.

*Gastric emptying studies:* Gastric emptying is delayed by codeine so gastric emptying studies will not be valid.

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## **Adverse Effects**

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Reports of adverse reactions are rare. Although the following reactions have been reported when paracetamol and codeine have been administered:

### **Haematologic**

Less frequent to rare: agranulocytosis, anaemia, thrombocytopenia.

### **Genitourinary**

Less frequent to rare: renal failure, uraemia, urinary retention or hesitance.

### **Hypersensitive**

Less frequent to rare: skin rashes and other allergic reactions, histamine release (hypotension, flushing of the face, tachycardia, breathlessness).

### **Gastrointestinal**

Common: constipation, nausea, vomiting.

### **Neurological**

Common: drowsiness, dizziness.

Less frequent to rare: euphoria, dysphoria, at higher doses codeine may cause respiratory-depression.

### **Hepatic**

Very rare: pancreatitis

Paracetamol has also been associated with dyspepsia, sweating, angioneurotic oedema, leukopenia, agranulocytosis and pancytopenia. Bronchospasms may be triggered in patients having a tendency of analgesic asthma.

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## Dosage and Administration

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### Adults and Children over 12 years

1-2 tablets every 4-6 hours with water as required (maximum 8 tablets in 24 hours).

### Children 7 – 12 years

½ to 1 tablet every 4-6 hours with water as required (maximum 4 tablets in 24 hours).

### Children under 7 years

Not suitable.

Do not use for more than 48 hours in children aged 7 to 17, or more than a few days at a time in adults, except on medical advice.

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## Overdosage

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### *Symptoms*

Toxic symptoms include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma.

The most serious adverse effect of acute overdosage of paracetamol is a dose-dependent, potentially fatal hepatic necrosis. In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 g (30 tablets) of paracetamol; a dose of 25 g (50 tablets) or more is potentially fatal. Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to develop.

In an evaluation of codeine intoxication in children, symptoms seen included: sedation, rash, miosis, vomiting, itching, ataxia and swelling of the skin. Respiratory failure may occur.

### *Treatment*

Consists primarily of management of paracetamol toxicity; naloxone is the treatment of choice for codeine intoxication. In cases of overdosage, methods of reducing the absorption of ingested drug are important. Prompt administration of 50 g activated charcoal and 500 mL iced mannitol 20% by mouth may reduce absorption.

If the history suggests that 15 g paracetamol or more has been ingested, administer one of the following antidotes:

#### Acetylcysteine 20% i.v

Administer 20% acetylcysteine (Parvolex, David Bull) immediately without waiting for positive urine test or plasma level results: initial dose 150 mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in 500 mL 5% glucose over 4 hours and 100 mg/kg in 1L 5% glucose over 16 hours; or

#### Oral Methionine

2.5 g immediately followed by three further doses of 2.5 g at four hourly intervals. For a 3-year-old child, 1g methionine 4-hourly for four doses has been used.

If more than ten hours have elapsed since the overdosage was taken, the antidote may be ineffective. When treatment for paracetamol toxicity has been initiated; naloxone 400 microgram may be administered SC, IM or IV; IV may be repeated at intervals of 2 to 3 minutes if necessary.

Assisted respiration may be required.

Contact the Poisons Information Centre on **0800 764 766** or **0800 POISON** for advice on the treatment and management of any overdose.

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## **Pharmaceutical Precautions**

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### ***Shelf life and Special Precautions for Storage***

2 years. Store at or below 30°C.

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## **Medicine Classification**

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Pharmacist Only Medicine: 20 & 40 packs, Prescription Medicine: 100 pack.

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## **Package Quantities**

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Available in blister packs of 20, 40 & 100 tablets.

Not all pack sizes may be marketed.

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## **Name and Address**

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Arrow Pharmaceuticals (NZ) Ltd.  
Mt Eden Central Business Park  
33a Normanby Road, Mt Eden  
Auckland, New Zealand

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## **Date of Preparation**

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14 April 2011