AUSTRALIAN PRODUCT INFORMATION – <MEDICINE NAME>

# NAME OF THE MEDICINE

Paracetamol

# QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet/ capsule contains paracetamol 500mg.

<Excipients of known effect>

For the full list of excipients see **section 6.1 List of Excipients.**

# PHARMACEUTICAL FORM

<Visual ID as per ARTG record>.

# CLINICAL PARTICULARS

## THERAPEUTIC INDICATIONS

<Indications as per ARTG record>.

## DOSE AND METHOD OF ADMINISTRATION

<Directions as per ARTG record (e.g. labelling)> *OR*

**Adults and children 12 years of age and over:** 1 to 2 tablets/ capsules every four to six hours. Maximum of 8 tablets/ capsules in 24 hours. Maximum daily dose: 4000 mg (8 tablets/ capsules).

**Children 7 to 12 years:** ½ to 1 tablet/capsule every four to six hours. Maximum of 4 tablets/capsules in 24 hours.

**Children under 7 years:** Not recommended for children under 7 years.

## CONTRAINDICATIONS

This medication is contraindicated in patients who are hypersensitive to paracetamol or to any of the excipients in this medicine.

## SPECIAL WARNINGS AND PRECAUTIONS FOR USE

This medication may be dangerous when used in large amounts or for long periods. Hepatotoxicity may occur with paracetamol even at therapeutic doses, after short treatment duration and in patients without pre-existing liver dysfunction. Hepatotoxicity may develop following as little as 10 to 15g of paracetamol and hepatic failure is known to occur occasionally with long term use of paracetamol. To avoid the risk of overdose do not use with other paracetamol containing products.

Caution is advised in patients with underlying sensitivity to aspirin and/or to non-steroidal anti-inflammatory drugs (NSAIDs).

Patients with known analgesic intolerance or known bronchial asthma must only use this medication after having consulted a physician (hypersensitivity reactions including bronchospasm are possible).

Severe cutaneous adverse reactions (SCARs): Life threatening cutaneous reactions Stevens-Johnson Syndrome (SJS), and Toxic Epidermal Necrolysis (TEN) have been reported with the use of paracetamol. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms or signs of SJS and TEN (e.g. progressive skin rash often with blisters or mucosal lesions) occur, patients should stop paracetamol treatment immediately and seek medical advice.

Paracetamol should be used upon medical advice in patients with Gilbert’s syndrome or glucose – 6 –phosphate – dehydrogenase deficiency.

### Use in hepatic impairment

Paracetamol should be used with caution in patients with impaired liver function: Underlying liver disease increases the risk of paracetamol-related liver damage.

Patients who have been diagnosed with liver impairment must seek medical advice before taking this medication.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index, are chronic heavy users of alcohol or have sepsis.

In patients with glutathione depleted states the use of paracetamol may increase the risk of metabolic acidosis.

### Use in renal impairment

Paracetamol should be used with caution in patients with impaired kidney function: Administration of paracetamol to patients with moderate to severe renal impairment may result in accumulation of paracetamol conjugates.

Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medication.

### Use in the elderly

No data available.

### Paediatric use

Not recommended for children under 7 years of age.

### Effects on laboratory tests

*Uric acid and blood glucose:* Intake of paracetamol may affect the laboratory determination of uric acid by phosphotungstic acid and of blood glucose by glucose oxidase-peroxidase.

## INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

* **Anticoagulants:** Paracetamol may increase the risk of bleeding in patients taking warfarin and other antivitamin K medicines. Anticoagulant dosage may require reduction and patients should be monitored for appropriate coagulation and bleeding complications.
* **Cholestyramine:** reduces the absorption of paracetamol if given within 1 hour of paracetamol. Chelating resins can decrease the intestinal absorption of paracetamol and potentially decrease its efficacy if taken simultaneously. In general, there must be an interval of more than 2 hours between taking the resin and taking paracetamol, if possible.
* **Drugs which affect motility**:
  + Paracetamol absorption is increased by drugs which increase gastric emptying e.g. metoclopramide and domperidone
  + Paracetamol absorption is decreased by drugs which decrease gastric emptying such as propantheline, antidepressants with anticholinergic properties, and narcotic analgesics.
* **Glutathione depletion states:** Co-administration of paracetamol and flucloxacillin may lead to metabolic acidosis, particularly in patients presenting risk factors of glutathione depletion, such as sepsis, malnutrition or chronic alcoholism.
* **Hepatotoxic drugs and microsomal liver enzyme inducers/ inhibitors (CYP1A2)**: The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic drugs or drugs that induce liver microsomal enzymes, such as antiepileptics (such as phenobarbital, phenytoin, carbamazepine, topiramate), alcohol, barbiturates and rifampicin. The induced metabolism results in an elevated production of the hepatotoxic oxidative metabolite of paracetamol. Hepatotoxicity will occur if this metabolite exceeds the normal glutathione binding capacity.
* **Probenecid:** Paracetamol excretion may be affected, and plasma concentrations altered, by probenecid treatment.

## FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

No data available.

### Use in pregnancy – Pregnancy Category A

Drugs which 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. Paracetamol can be used during pregnancy if clinically needed however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Paracetamol can cross the placenta; however, no teratogenic effects have been observed in rats or mice, after doses of up to 250mg/kg.

A woman in the third trimester of pregnancy ingested 22.5 g paracetamol. Early treatment with oral acetylcysteine resulted in good outcome for both mother and foetus.

### Use in lactation

Paracetamol is excreted in breast milk. The amount available for ingestion by the infant has been reported variously as less than 0.1% of a single 500 mg dose and as 0.04 to 0.23% of a single 650 mg dose. Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the nursing infant. Available published data do not contraindicate breastfeeding.

## EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

## ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse effects associated with the use of paracetamol are rare.

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| --- | --- |
| **Frequency** | **Adverse effect** |
| Common (>1%) | increased aminotransferases |
| Rare (<0.1%) | acute hepatitis, dyspepsia |
| Very rare (<0.01%) | hypersensitivity reactions (eg anaphylactic shock, angioneurotic oedema, difficulty breathing, drop in blood pressure, nausea, rash, fixed drug eruption, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome; haematological reactions, including thrombocytopenia, leukopenia, neutropenia, agranulocytosis and pancytopenia |

Bronchospasm may be triggered in patients having a tendency of analgesic asthma.

Haemolytic anaemia, particularly in patients with underlying glucose 6-phosphate-dehydrogenase deficiency has been reported. Kounis syndrome has been reported, as has pyroglutamic acidosis in patients with pre-disposing factors for glutathione depletion.

### Reporting suspected adverse effects

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>

## OVERDOSE

Elderly persons, small children, patients with liver disorders, chronic alcohol consumption or chronic malnutrition, as well as patients concomitantly treated with enzymes-inducing drugs are at an increased risk of intoxication, including fatal outcome. Overdosage with paracetamol if left untreated can result in severe, sometimes fatal liver damage and rarely, acute renal tubular necrosis.

### Symptoms

Immediate medical management is required in the event of an overdose, even if the symptoms of overdose are not present.

Toxic symptoms include vomiting, abdominal pain, hypotension and sweating. Nausea, vomiting, anorexia, pallor and abdominal pain generally appear during the first 24 hours of overdosage with paracetamol. Overdosage with paracetamol may cause hepatic cytolysis which can lead to hepatocellular insufficiency, gastrointestinal bleeding, metabolic acidosis, encephalopathy, disseminated intravascular coagulation, coma and death. Increased levels of hepatic transaminases, lactate dehydrogenase and bilirubin with a reduction in prothrombin level can appear 12 to 48 hours after acute overdosage. Overdosage can also lead to pancreatitis acute renal failure and pancytopenia. The most serious adverse effect of acute overdosage of paracetamol is a dose-dependent, potentially fatal hepatic necrosis.

### Treatment

If an overdose is taken or suspected, contact the Poisons Information Centre immediately for advice (131 126), or the patient should go to the nearest hospital straight away. This should be done even if they feel well because of the risk of delayed, serious liver damage.

# PHARMACOLOGICAL PROPERTIES

## PHARMACODYNAMIC PROPERTIES

### Mechanism of action

Paracetamol has analgesic and antipyretic effects.

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. It does not possess anti-inflammatory activity. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. The lack of peripheral prostaglandin inhibition confers important pharmacological properties such as the maintenance of the protective prostaglandins within the gastrointestinal tract. Paracetamol is therefore particularly suitable for patients with a history of acid peptic disease, or on concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or in the elderly).

### Clinical trials

No data available.

## PHARMACOKINETIC PROPERTIES

### Absorption

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 10 to 60 minutes after oral administration. Food intake delays paracetamol absorption.

### Distribution

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 breast milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

### Metabolism

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.

### Excretion

Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol. 85-90% of the administered dose is eliminated in the urine within 24 hours of ingestion. The elimination half-life is about 1 to 4 hours.

## PRECLINICAL SAFETY DATA

### Genotoxicity

No data available.

### Carcinogenicity

No data available.

# PHARMACEUTICAL PARTICULARS

## LIST OF EXCIPIENTS

<List of excipients>

## INCOMPATIBILITIES

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

## SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## SPECIAL PRECAUTIONS FOR STORAGE

<Approved storage conditions>

## NATURE AND CONTENTS OF CONTAINER

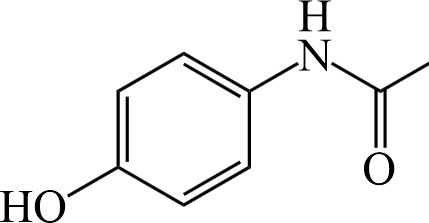
<As per ARTG entry>

## SPECIAL PRECAUTIONS FOR DISPOSAL

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

## PHYSICOCHEMICAL PROPERTIES

### Chemical structure

Chemical Name: N-acetyl-p-aminophenol. Structural Formula:

Molecular formula: C8H9NO2

Molecular weight: 151.17

CAS number: 103-90-2

# MEDICINE SCHEDULE (POISONS STANDARD)

<Blister packs: Packs of 16 – Not scheduled

Packs more than 16 to less than 50 dosage units – S2, Pharmacy Medicine

Packs of more than 50 – S3, Pharmacist Only Medicine

Bottles: S3, Pharmacist Only Medicine>

# SPONSOR

<Sponsor details>

# DATE OF FIRST APPROVAL

<Date>.

# DATE OF REVISION

TBC

**Summary table of changes**

|  |  |
| --- | --- |
| **Section Changed** | **Summary of new information** |
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