AUSTRALIAN PRODUCT INFORMATION
PARACETAMOL OSTEO-TAB (PARACETAMOL) MODIFIED RELEASE TABLET

1. NAME OF THE MEDICINE

Paracetamol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Paracetamol 665 mg/tablet

Excipient with known effect: Lactose monohydrate (present in the film coating Opadry II).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white capsule shaped, biconvex, film coated tablets. Embossed with ML 77 on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paracetamol Osteo-Tab provides effective relief from persistent pain for up to 8 hours. Effective for the relief of persistent pain associated with osteoarthritis and muscular aches and pains such as backache. Provides effective temporary relief of pain and discomfort associated with: headache, tension headache, cold and flu, period pain, toothache and pain after dental procedures. Reduces fever.

4.2 Dose and method of administration

Dose

Adults and children aged 12 years and over

2 tablets swallowed whole three times a day every 6 to 8 hours. Maximum of 6 tablets in 24 hours.

Minimum dosing interval: 6 hours.

Maximum daily dose for children 12 years of age to adults: 6 tablets.

Should not be used for more than 48 hours for children aged 12 – 17 years except on medical advice.

Not recommended for children under the age of 12 years.

Do not exceed the stated dose.

Doses should be equally spaced throughout the day.

Do not use for more than a few days at a time except on medical advice.

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

Should not be used with other paracetamol-containing products.

Special populations
Renal impairment
See section 4.4 Special warnings and precautions for use.

Hepatic impairment
See section 4.4 Special warnings and precautions for use.

Method of administration

To be taken orally with or without food.

Take with water or other fluid.

The tablets must not be crushed, chewed or sucked as it impairs the sustained release properties.

4.3 Contraindications

Paracetamol Osteo-Tab is contraindicated in patients with a previous history of hypersensitivity to paracetamol or to any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

High Anion Gap Metabolic Acidosis
Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or patients with malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

Hepatotoxicity
Contains paracetamol. Do not use with any other paracetamol- containing products. The concomitant use with other products containing paracetamol may lead to an overdose.

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.
If symptoms persist, medical advice must be sought.

Keep out of sight and reach of children.

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 the age of 12 years.

Effects on laboratory tests
No data available.

4.5 Interaction with other medicines and other forms of interaction

The following interactions with paracetamol have been noted:

The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect. Anticoagulant 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.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4).

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.

4.6 Fertility, pregnancy and lactation

Effects on fertility
No data available.

Use in pregnancy – Category A
Paracetamol has 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.

As with the use of any medicine during pregnancy, pregnant women should seek medical advice before taking paracetamol. The lowest effective dose and shortest duration of treatment should be considered.

Use in lactation
Paracetamol is excreted in breast milk. Human studies with paracetamol have not identified any risk to lactation or the breast-fed offspring. These results are based on immediate release preparations of paracetamol. There is no data available on the excretion of sustained-release paracetamol preparations in breast milk. However, it is not expected that Paracetamol Osteo-Tab would provide any increase in the excretion of paracetamol in breast milk as this product is designed to maintain rather than increase plasma paracetamol concentrations compared to immediate release preparations. Maternal ingestion of paracetamol in usual analgesic doses does not appear to present a risk to the breastfed infant.

4.7 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.

4.8 Adverse effects (Undesirable effects)

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 https://www.tga.gov.au/reporting-problems.

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled doses and considered attributable are tabulated below by System Organ Class and frequency.

The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from available data).

High anion gap metabolic acidosis with frequency "Not known" (cannot be estimated from the available data): Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

Adverse event frequencies have been estimated from spontaneous reports received through post-marketing data.

Table 1: Post marketing data

Body System	Undesirable Effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Very rare
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes, angioedema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis.	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm, especially in patients sensitive to aspirin and other NSAIDS	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare

4.9 Overdose

Poisons Information Centre
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 (see Adverse effects). Because

Paracetamol Osteo-Tab is a sustained-release formulation of paracetamol, absorption will be prolonged in overdose. It is recommended that for the management of overdose, where Paracetamol Osteo-Tab is suspected, that an additional plasma paracetamol level be obtained 4-6 hours after the initial

measurement. If either level is above or close to the treatment line on the paracetamol overdose nomogram, administration of antidote would be indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. It does not possess anti-inflammatory activity. It provides relief from mild to moderate pain and fever.

The combination of immediate release and sustained release paracetamol provides pain relief, which may last up to 8 hours.

Clinical trials

Chronic Pain

In patients with pain associated with osteoarthritis of the knee, modified release paracetamol (2 tablets taken three times daily) and standard immediate release paracetamol (2 tablets taken 4 times daily) were clinically equivalent at a total daily dose of 4 g based on patient global assessment after treatment for 7 days. Modified release paracetamol and standard immediate release paracetamol were not significantly different for a range of secondary efficacy parameters including pain during the day, pain on walking, pain relief, number of times woken during the night due to pain and duration of morning stiffness.
Since modified release paracetamol (three times daily) was clinically equivalent to standard immediate release paracetamol (four times daily), it was concluded that modified release paracetamol provides pain relief for up to 8 hours after dosing.

Acute Pain

In patients with post-surgical dental pain, a single dose of modified release paracetamol (2 tablets) was therapeutically equivalent to standard immediate release paracetamol (2 tablets) based on patient global assessment 4 hours after treatment. Onset of action was apparent 30 minutes after administration. There was no significant difference between modified release paracetamol and standard immediate release paracetamol in either development of analgesia or peak analgesic effect. Trends in favour of modified release paracetamol were observed at the later time points. Furthermore, modified release paracetamol was significantly more effective than standard immediate release paracetamol for the summed pain intensity difference at 6 hours ($p = 0.0344$) and 8 hours ($p = 0.0500$), as measured on a visual analogue scale.

Summary

From these results, it was concluded that modified release paracetamol has a similar time to onset of action compared to standard immediate release paracetamol and provides more prolonged analgesia than standard immediate release paracetamol. For the patient, this translates to longer lasting pain relief and the improved convenience of fewer doses. This is as expected for a formulation containing sustained release paracetamol and consistent with results from the pharmacokinetic studies.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Food intake delays paracetamol absorption.

Distribution
Paracetamol is distributed into most body tissues. Binding to the plasma proteins is minimal at therapeutic concentrations but increases with increasing doses.

Metabolism
Paracetamol is metabolised in the liver. 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 200 mg/kg or 10 g total paracetamol ingested) and, if left untreated, can cause irreversible liver damage.

Paracetamol is metabolised differently by infants and children compared to adults, the sulphate conjugate being predominant.

Excretion
Paracetamol is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unmodified paracetamol with 85% to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from one to three hours.

5.3 Preclinical safety data

Genotoxicity
No data available

Carcinogenicity
No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, Hypromellose, Opadry II film coating (contains lactose monohydrate), magnesium stearate, microcrystalline cellulose, povidone, pregelatinised maize starch.

6.2 Incompatibilities

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

6.3 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.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

PVC/PVDC/Al blister packs of 48 and 96 tablets.

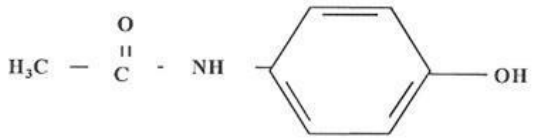
HDPE bottles of 96, 100 and 1000 tablets.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



CAS number

103-90-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S3-Pharmacist Only Medicine

8. SPONSOR

9.

AFT Pharmaceuticals Pty Ltd
113 Wicks Road
North Ryde
NSW 2113
AUSTRALIA
Phone: 1800 238 74276

Email: customer.service@aftpharm.com

10. DATE OF FIRST APPROVAL

19 January 2012

11. DATE OF REVISION

12 June 2025

Summary table of changes

Section changed	Summary of new information
4.4, 4.5, 4.8	Safety related update