NEW ZEALAND DATA SHEET
PARACETAMOL OSTEO-TAB TABLETS 665 mg

1 NAME OF THE MEDICINE

Paracetamol Osteo-Tab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Paracetamol 665 mg/tablet

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

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

3 PHARMACEUTICAL FORM

White to off-white capsule shaped, 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

Adults and children aged 12 years and over: 2 tablets swallowed whole three times a day every 6 to 8 hours. Do not chew or suck, as it impairs the sustained release properties. Maximum of 6 tablets in 24 hours.

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

Not recommended for children under the age of 12 years.

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

Take with water or other fluid.

Can be taken with or without food.

Doses should be equally spaced throughout the day. The tablets must not be crushed, chewed or sucked as it impairs the sustained release properties.

Do not exceed the stated dose.

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.

Minimum dosing interval: 6 hours.

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

4.3 CONTRAINDICATIONS

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

Identified precautions

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 12 years of age.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

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 – 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 https://nzphvc.otago.ac.nz/reporting/}

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).

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

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death. Acute pancreatitis has been observed with hepatic dysfunction and liver toxicity.

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

If an overdose is taken or suspected, contact the Poisons Information Centre immediately for advice (0800 764 766), 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.

In cases of overdose, methods of reducing absorption of ingested drug are important. Activated charcoal may reduce absorption of the medicine if given within two hours after ingestion.

Because Paracetamol Osteo-Tab is a sustained-release formulation of paracetamol, absorption will be prolonged in overdose, the maximum plasma concentration may occur later, and high concentrations, in particular after large doses, may persist for several days.

The usual protocols of sampling and treatment regimens used in the management of overdose with immediate release paracetamol formulations are therefore not adequate.

Where overdose with ≥10 g Paracetamol Osteo-Tab is known or suspected, or where dose is unknown, treatment with antidote (usually N-acetylcysteine) should be started immediately. Refer to the acetylcysteine data sheet for information on administration.

Where < 10 g Paracetamol Osteo-Tab has been ingested and time since ingestion is unknown, multiple serum paracetamol samples should be taken at suitable intervals (e.g. 4, 6, and 8 hours after ingestion). Further samples should be considered if serum paracetamol concentrations are not declining. If serum paracetamol levels exceed the treatment nomogram at any timepoint, treatment with antidote (usually N-acetylcysteine) is indicated. Refer to the acetylcysteine data sheet for information on administration.

If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (usually N-acetylcysteine). Refer to the acetylcysteine data sheet for information on administration.

Further information on the management of modified-release paracetamol overdose can be found in the “Guidelines for the management of paracetamol poisoning in Australia and New Zealand” available at https://www.mja.com.au/sites/default/files/issues/203_05/Guidelines_paracetamol_Aus_NZ_2015.pdf.

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.

Bioequivalence
Paracetamol Osteo-Tab, releases drug at a rate which ensures that therapeutically active plasma paracetamol concentrations are rapidly attained and maintained until up to 8 hours after administration.

Paracetamol Osteo-Tab and standard immediate release paracetamol were bioequivalent in volunteers with respect to dose-corrected $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$ in both the fed and fasted states following administration of a single dose. This indicates that the extent of paracetamol absorption from Paracetamol Osteo-Tab was equivalent to that of standard immediate release paracetamol. Food had little effect on the extent of paracetamol absorption from Paracetamol Osteo-Tab demonstrating that Paracetamol Osteo-Tab is suitable to be taken with or without meals. Paracetamol was rapidly absorbed after administration of the Paracetamol Osteo-Tab and was generally measurable in plasma within 15 minutes in fasted subjects. Mean plasma paracetamol concentrations above the minimum level required for analgesia (>4mcg/mL) were maintained until up to 6 to 7 hours after administration in fasted subjects and 7 to 8 hours in fed subjects.

At steady state, Paracetamol Osteo-Tab was bioequivalent with standard immediate release paracetamol based on the comparison of AUCs during the final 24 hour dosing period of the study. Furthermore, comparison of the pharmacokinetic parameters indicated that Paracetamol Osteo-Tab has the characteristics of a formulation containing sustained release paracetamol.

Fluctuations in the peak and trough values for plasma paracetamol concentrations were significantly smaller for Paracetamol Osteo-Tab than for standard immediate release paracetamol. Consequently, Paracetamol Osteo-Tab provided more consistent levels of paracetamol.

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

Data not available.

6.3 SHELF LIFE

36 months from date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

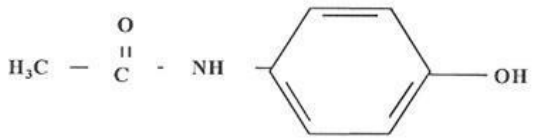
Packs of 12, 24, 48 and 96 tablets

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

Restricted

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 January 2012

10 DATE OF REVISION

March 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
2, 6.1	Correction of excipient “lactose monohydrate”