NEW ZEALAND DATA SHEET

1 PRODUCT NAME

APO-Paracetamol, 665 mg Modified release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 665mg of paracetamol (BP)

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

3 PHARMACEUTICAL FORM

White to off-white capsule shaped coated tablets with 665 debossed on one side and plain on other side. Tablet cannot be halved.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

APO-Paracetamol 665 mg is effective for the relief of persistent pain associated with osteoarthritis and muscle aches and pains such as backache. APO-Paracetamol 665 mg also provides effective, temporary relief of pain and discomfort associated with headache, tension headache, period pain, toothache and pain after dental procedures, and cold & flu. 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. 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.
Children under 12 years: Not recommended for children under the age of 12 years.
Should not be used for more than 48 hours for children 12 – 17 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. Minimum dosing interval 6 hours. The tablets must not be crushed.

Do not exceed the stated dose.

Should not be used with other paracetamol-containing products.

Renal and Hepatic impairment

Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication. (See **section 4.4** Special Warnings and precautions for use.)

4.3 CONTRAINDICATIONS

Paracetamol is contraindicated in patients with a previous history of hypersensitivity to paracetamol or any of the excipients listed below.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Keep out of sight and reach of children.

Use in hepatic impairment

Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with liver or kidney 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 max 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.

If symptoms persist, medical advice must be sought.

Experience following overdose with paracetamol indicates that the clinical signs of liver injury occur usually after 24 to 48 hours and have peaked usually after 4 to 6 days.

Because Paracetamol 665 mg modified release tablet 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 regimen used in the management of overdose with immediate release paracetamol formulations are therefore not adequate.

Refer to **section 4.9** Overdose if overdose is confirmed or suspected.

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 665 mg modified release tablet medication is prolonged.

Paracetamol absorption is increased by substances that increase gastric emptying, eg metoclopramide.

Paracetamol absorption is decreased by substances that decrease gastric emptying, eg 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 drugs.

Paracetamol excretion may be affected and plasma concentrations altered when given with probenecid.

Colestyramine reduces the absorption of paracetamol if given within one hour of paracetamol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Not data available

Use in pregnancy – Pregnancy Category A

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.

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.

Paracetamol crosses the placental barrier. Animal studies with paracetamol have not identified any risk to pregnancy or embryo-foetal development.

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 are no data available on the excretion of sustained-release paracetamol preparations in breast milk. However, it is not expected that Paracetamol 665 mg modified release tablet 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.

Available published data do not contraindicate breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Paracetamol 665 mg modified release tablet is unlikely to cause an effect on the ability to drive or use machinery.

4.8 UNDESIRABLE EFFECTS

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 dose 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.

Body System	Undesirable Effect	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Very rare
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including 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

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at http://nzphvc.otago.ac.nz/reporting/

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.

Treatment

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. (See section 4.8 Undesirable effects)

Administration of N-acetylcysteine or methionine may be required.

In cases of overdosage, methods of reducing absorption of ingested drug are important. Activated charcoal may reduce absorption of the medicine if given within one hour after ingestion.

Because Paracetamol 665 mg modified release tablet 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 regimen used in the management of overdose with immediate release paracetamol formulations are therefore not adequate.

Where < 10g Paracetamol 665mg have 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.

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764766).

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 is given by mouth or rectally (suppositories) for mild to moderate pain and fever.

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 disease or on concomitant medication, where peripheral prostaglandin inhibition would be undesirable (such as, for example, those with a history of gastrointestinal bleeding or the elderly).

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

Chronic Pain

In patients with pain associated with osteoarthritis of the knee, paracetamol 665 mg modified release tablets (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.

Paracetamol 665 mg modified release tablet 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 or morning stiffness.

Since paracetamol 665 mg modified release tablet (three times daily) was clinically equivalent to standard immediate release paracetamol (four times daily), it was concluded that paracetamol 665 mg modified release tablet provides pain relief for up to 8 hours after dosing.

Acute Pain

In patients with post-surgical dental pain, a single dose of paracetamol 665 mg modified release tablet (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 paracetamol 665 mg modified release tablet and standard immediate release paracetamol in either development of analgesia or peak analgesic effect. Trends in favour of paracetamol 665 mg modified release tablet were observed at the later time points. Furthermore, paracetamol 665 mg modified release tablet 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 paracetamol 665 mg modified release tablet 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.

Paracetamol 665 mg modified release tablet is a unique bi-layer tablet incorporating an immediate release and a sustained release dose of paracetamol.

The sustained release layer contains HPMC polymer, which rapidly hydrates to form a gel layer at the matrix periphery. The drug is then released from the matrix by a combination of diffusion and erosion of the gel layer.

Paracetamol 665 mg modified release tablet releases drug at a rate that ensures that a mean plasma therapeutic level of 4µg/mL paracetamol is maintained until up to 8 hours after administration.

Paracetamol 665 mg modified release tablet and standard immediate release paracetamol were bioequivalent in volunteers with respect to dose-corrected AUC(0-t) and AUC(0-inf) in both the fed and fasted states following administration of a single dose. This indicates that the extent of paracetamol absorption from paracetamol 665 mg modified release tablet was equivalent to that of standard immediate release paracetamol. Food had little effect on the extent of paracetamol absorption from paracetamol 665 mg modified release tablets demonstrating that paracetamol modified release tablet is suitable to be taken with or without meals. Paracetamol was rapidly absorbed after administration of paracetamol 665 mg modified release tablet 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 665 mg modified release tablet 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 665 mg modified release tablet 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 665 mg modified release tablet than for standard immediate release paracetamol (mean fluctuation index = 0.957 and 1.388, respectively, $p<0.001$), indicating that this paracetamol 665 mg modified release tablet provided more consistent levels of paracetamol. Compared to the standard immediate release paracetamol, Paracetamol 665mg modified release tablets provided a lower mean C_{max} (>4µg/mL) and slightly great C_{min}.

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

Preclinical safety data on paracetamol in the literature have not revealed findings that are of relevance to the recommended dosage and use of the product.

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain maize starch, sodium starch glycollate (Type A), colloidal anhydrous silica, povidone, magnesium stearate, pregelatinised maize starch, hypromellose, microcrystalline cellulose, macrogol 6000, purified talc, titanium dioxide.

6.2 INCOMPATIBILITIES

Not known

6.3 SHELF LIFE

24 months from manufacture

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/aluminium foil blister packs of 96 modified release tablets and HDPE bottle pack of 100 modified release tablets.

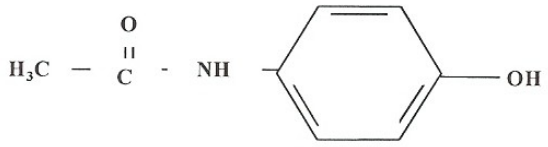
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL <AND OTHER HANDLING>

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

Pharmacy only

8 SPONSOR

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9 DATE OF FIRST APPROVAL

15 January 2024

10 DATE OF REVISION OF THE TEXT

15 January 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat
4.4	Addition of concomitant use with paracetamol, Update to use in hepatic impairment
4.6	Update to Use in pregnancy and Use in lactation
4.8	Addition of adverse effects: Toxic Epidermal Necrolysis and update to Bronchospasm.
4.9	Update to paracetamol overdose
5.2	Update to absorption and distribution.