NEW ZEALAND DATA SHEET

1. PRODUCT NAME

PANADOL OSTEO modified-release tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
Paracetamol (BP) 665 mg/tablet

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

3. PHARMACEUTICAL FORM

Film-coated, bi-layer capsule-shaped tablets.
White to off-white tablets with flat edges. Embossed with the logo "8" on the front face and plain on the back face. Tablet cannot be halved.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PANADOL OSTEO is effective for the relief of persistent pain associated with osteoarthritis and muscle aches and pains such as backache. PANADOL OSTEO 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 caplets swallowed whole three times a day every 6 to 8 hours. Maximum of 6 caplets 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. Do not chew or suck, as it impairs the sustained release properties.

Can be taken with or without food.

Doses should be equally spaced throughout the day. Minimum dosing interval 6 hours.

The caplets must not be crushed.

Do not exceed the stated dose.

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

Minimum dosing interval: 6 hours

Should not be used with other paracetamol-containing products.

4.3 Contraindications

This product is contraindicated in patients with a previous history of hypersensitivity to paracetamol or any of the excipients.

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.

Paracetamol overdose may cause liver failure which may require liver transplant or lead to death.

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 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.

If symptoms persist, medical advice must be sought.

Keep out of sight and reach of children.

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 tablets are a sustained-release product, 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.

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 PANADOL OSTEO 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 Pregnancy and lactation

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.

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 PANADOL OSTEO 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

PANADOL OSTEO 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, 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

Reporting of suspected adverse reactions

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 https//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.

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 PANADOL OSTEO 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 PANADOL OSTEO 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 PANADOL OSTEO 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.

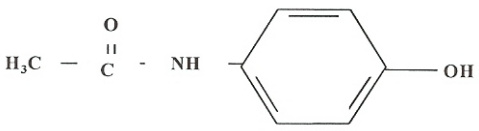
If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (usually N-acetylcysteine). Refer to the acetylcysteine data sheet for information on administration.

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

CAS: 103-90-2 (paracetamol)



Paracetamol MW 151.17
ATC code Paracetamol, N02BE01

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, PANADOL OSTEO (2 caplets taken three times daily) and standard immediate release paracetamol (2 caplets 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.

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

Acute Pain
In patients with post-surgical dental pain, a single dose of PANADOL OSTEO (2 caplets) was therapeutically equivalent to standard immediate release paracetamol (2 caplets) based on patient global assessment 4 hours after treatment. Onset of action was apparent 30 minutes after administration.

There was no significant difference between PANADOL OSTEO and standard immediate release paracetamol in either development of analgesia or peak analgesic effect. Trends in favour of PANADOL OSTEO were observed at the later time points. Furthermore, PANADOL OSTEO 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 PANADOL OSTEO 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.

PANADOL OSTEO is a unique bi-layer caplet 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.

PANADOL OSTEO releases drug at a rate that ensures that a mean plasma therapeutic level of 4 µg/mL paracetamol is maintained up to 8 hours after oral administration.

PANADOL OSTEO was shown to be bioequivalent to standard immediate release paracetamol, based on a comparison of the AUCs during the evaluation period 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 PANADOL OSTEO was equivalent to that of standard immediate release paracetamol. Food had little effect on the extent of paracetamol absorption from PANADOL OSTEO demonstrating that PANADOL OSTEO is suitable to be taken with or without meals. Paracetamol was rapidly absorbed after administration of PANADOL OSTEO and was generally measurable in plasma within 15 minutes in fasted subjects. Mean plasma paracetamol concentrations above the minimum level required for analgesia (>4 µg/mL) were maintained for up to 6 to 7 hours after administration in fasted subjects and 7 to 8 hours in fed subjects.

At steady state, PANADOL OSTEO 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 PANADOL OSTEO has the characteristics of a formulation containing sustained release paracetamol.

Fluctuations in the peak and trough were significantly smaller for PANADOL OSTEO (p,0.001), indicating that this formulation provided a more consistent level of paracetamol. Compared to the standard immediate release paracetamol, PANADOL OSTEO provided a lower mean C_{max} (>4 µg/mL) and slightly greater 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, Pregelatinised maize starch, Povidone, Croscarmellose sodium, Magnesium stearate, Stearic acid, Glycerol Triacetate, Carnauba wax

6.2 Incompatibilities
Not known.

6.3 Shelf life
4 years from date of manufacture.

6.4 Special precautions for storage
Store below 30ºC.

6.5 Nature and contents of container
Blister packs of 6, 12 and 96 caplets.
(Not all pack sizes may be marketed.)

7. MEDICINE SCHEDULE

Restricted

8. SPONSOR

GlaxoSmithKline Consumer Healthcare,
11th Floor, Zurich House,
21 Queen St
Auckland 1010, New Zealand
Tel 09 367 2900

9. DATE OF FIRST APPROVAL
10 April 2008

10. DATE OF REVISION OF TEXT
06 January 2020

Summary table of changes

Section changes	Summary of new changes
6.5	Add pack size 12 caplets.