

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

PANADOL® Extra (reformulation), Paracetamol 500 mg and Caffeine 65 mg, film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients:

Paracetamol 500mg & Caffeine 65mg caplets

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

White to off-white, oval shape, debossed with a logo "P" in a circle on one side and a deep score line on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

PANADOL EXTRA (reformulation) is indicated for the temporary relief of pain and discomfort associated with headache, tension headache, migraine headache, osteoarthritis, arthritis, cold & flu symptoms, toothache, dental procedures, muscular aches, sore throat and period pain. Reduces fever.

4.2. Dosage and Method of Administration

PANADOL EXTRA (reformulation) is to be administered orally, with or without food. For Adults and children 12 years and older: 2 caplets every 4 to 6 hours (as required). Maximum of 8 caplets in 24 hours. Not recommended in children under the age of 12 years.

Take with water or other fluid.

Can be taken with or without food.

The caplets must not be crushed.

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: 4 hours.

Maximum daily dose: 4000 mg paracetamol.

4.3. Contraindications

This product is contraindicated in patients with hypersensitivity to paracetamol, caffeine or to 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.

Paracetamol should be used with caution in patients with:

- Impaired liver function: Underlying liver disease increases the risk of paracetamol-related liver damage
- 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 liver or kidney impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with liver or kidney impairment are primarily a consequence of the paracetamol content of the drug.

Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product.

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.

Use in Children: Not recommended in children under the age of 12 years.

4.5. Interactions with Other Medicines and Other Forms of Interaction

The anticoagulant effect of warfarin and other coumarins can be enhanced by prolonged regular daily use of paracetamol with an increased risk of bleeding; occasional doses have no significant effect. Paracetamol absorption is increased by drugs which increase gastric emptying, eg metoclopramide, and decreased by drugs which decrease gastric emptying, eg propantheline, antidepressants with anticholinergic properties, narcotic analgesics. Paracetamol may increase chloramphenicol concentrations. The likelihood of paracetamol toxicity may be increased by the concomitant use of enzyme inducing agents such as alcohol or anticonvulsant drugs.

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

Colestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2, and is subject to numerous interactions with other drugs and substances which enhance or reduce its metabolic clearance.

No potentially hazardous interactions with caffeine have been reported. However patients who take medicines that decrease caffeine elimination may need to limit caffeine intake to avoid adverse events.

4.6. Fertility, Pregnancy and Lactation

Use in Pregnancy

The consumer should first seek medical advice before using PANADOL EXTRA (REFORMULATION).

Pregnancy Category A – Both Paracetamol and Caffeine have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations. Animal studies have shown an association between caffeine intake and foetal abnormalities, but only at very high doses that are not considered relevant to human consumption.

There is limited evidence that maternal caffeine intake during pregnancy may reduce birth weight. One review article indicated a correlation between caffeine consumption during pregnancy and a decrease in birth weight due to the vasoconstrictive effect of caffeine on placental circulation. Other reviews have found no correlation between caffeine intake in pregnancy and birth weight.

Paracetamol-caffeine is not recommended for use during pregnancy due to the possible increased risk of spontaneous abortion associated with caffeine consumption.

Use in Lactation

The consumer should first seek medical advice before using PANADOL EXTRA (REFORMULATION).

Paracetamol is excreted in breast milk but not in a clinically significant amount at recommended dosages. Available published data do not contraindicate breast-feeding. The amount available for ingestion by the infant has been reported variously as less than 0.1% of a single dose of paracetamol 500 mg 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 breastfed infant.

Caffeine is excreted in breast milk. Studies examining the transfer of caffeine into breast milk after oral doses of 35 to 336 mg of caffeine have recorded peak maternal plasma concentrations of 2.4 to 4.7 micrograms/mL, peak maternal saliva concentrations of 1.2 to 9.2 micrograms/mL, and peak breast-milk concentrations of 1.4 to 7.2 micrograms/mL. At these concentrations in breast milk, the calculated daily caffeine ingestion by breast-fed infants ranged from 1.3 to 3.1 mg, which was not thought to present a hazard, although irritability and a poor sleeping pattern have been reported.

The American Academy of Pediatrics states that caffeine is excreted slowly by the infant and may be associated with irritability and poor sleeping pattern when ingested by breast-feeding mothers. However, no effects occur with moderate intake of caffeinated beverages (2 to 3 cups daily) and caffeine is usually compatible with breast feeding.

4.7. Effects on ability to drive and use machines

PANADOL EXTRA (REFORMULATION) has no influence on the ability to drive or use machines.

4.8. Undesirable Effects

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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from available data)

Body System	Undesirable Effect	Frequency
Paracetamol		
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
Caffeine		
Central Nervous system	Nervousness Dizziness	Not known

When the recommended Panadol Extra dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

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

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

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

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

Administration of N-acetylcysteine may be required.

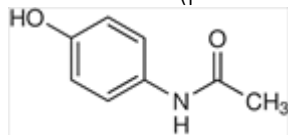
If an overdose is taken or suspected, the NZ National Poisons Centre should be contacted immediately for advice (call 0800 764 766), or the patient should go to a hospital straight away, even if they feel well, because of the risk of delayed, serious liver damage.

Caffeine overdose is rare. Early symptoms include insomnia, restlessness, excitement and may progress to mild delirium.

5. PHARMACOLOGICAL PROPERTIES

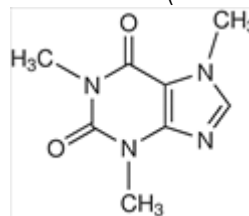
5.1. Pharmacodynamic Properties

CAS: 103-90-2 (paracetamol)



Paracetamol MW 151.17

CAS: 58-08-2 (caffeine)



Caffeine MW 194.20

Analgesic and antipyretic

ATC code Paracetamol & Caffeine, NO2BE51.

Mechanism of action

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. It inhibits prostaglandin synthetase in the hypothalamus, prevents synthesis of spinal prostaglandin and inhibits inducible nitric oxide synthesis in macrophages. Paracetamol has minimal anti-inflammatory action. Caffeine acts as an analgesic adjuvant which enhances the efficacy of paracetamol.

A meta-analysis to determine the analgesic effect of the combined dosage of paracetamol (1000mg) and caffeine (130mg) versus paracetamol (1000mg) alone has been undertaken. The primary outcome of the meta-analysis was to determine whether the use of paracetamol plus caffeine provided significantly superior analgesia over paracetamol alone in acute pain states.

Inclusion criteria were full journal publications reporting the results of randomised, controlled, double-blind trials comparing the two treatments.

The clinical measure selected was the >50% maxTOTPAR (i.e. the number of patients in the two groups who achieved at least 50% of the maximal pain relief). The dichotomous descriptor of >50% maxTOTPAR was chosen because it is a simple clinical end point of half pain relieved. It is a well-defined clinical measure of pain relief and can be used to evaluate the comparative benefit of contrasting medications.

Of the seven papers describing double blind trials, four papers met the inclusion criteria for the meta-analysis and contained eight separate studies. These eight studies spanned a number of different pain states; post-partum pain (n=3), headache (n=2), dental pain (n=2) and dysmenorrhoea (n=1).

All of the eight studies included in the meta-analysis provided efficacy results as mean TOTPAR values over 0-4-hours. The total number of patients evaluated was 1265 (paracetamol plus caffeine) and 1268 (paracetamol alone). Using the end-point of at least half pain relief achieved (at least 50%maxTOTPAR), the odds ratio of a greater likelihood of effect of the paracetamol/caffeine combination compared to paracetamol alone is 1.34 (95% CI 1.14, 1.58). This corresponds to a relative benefit of 1.12 (95% CI 1.05-1.19). Analgesic efficacy has also been determined as the number needed to treat (NNT). For the comparison of the paracetamol/caffeine combination with paracetamol alone, the NNT for at least 50% pain relief achieved over 0-4 hours is 14.

Compared with placebo, the relative benefit for the paracetamol/caffeine combination is 1.42 (95%CI 1.29-1.56) and the NNT for at least 50% pain relief achieved over 0-4 hours is 5. For paracetamol alone compared with placebo, the relative benefit is 1.27 (95%CI 1.15-1.40) and the NNT is 8¹.

The meta-analysis indicated that the combination of paracetamol and caffeine has an added benefit in analgesic activity compared to paracetamol alone.

Time effect curves for pain relief were presented in all eight of the studies included in the meta-analysis. Overall, these studies suggested that combining paracetamol with caffeine results in an earlier analgesic effect than is achieved with paracetamol alone.

5.2. Pharmacokinetic Properties

After oral administration, paracetamol is absorbed rapidly and completely from the gastrointestinal tract; peak plasma levels occur 10 to 60 minutes after administration.

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.

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45 to 55%) or sulfate (20 to 30%). A minor proportion (less than 20%) is metabolised to catechol derivatives and mercapturic acid compounds via oxidation. Paracetamol is excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol with 85 to 90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1 to 3 hours. Food intake delays paracetamol absorption.

Caffeine is absorbed readily after oral administration. Maximal plasma concentrations are achieved in adults within one hour and the plasma half-life is about 3 to 7 hours. Caffeine is almost completely metabolised in the liver by oxidation, demethylation and acetylation to various xanthine derivatives, which are excreted in the urine.

¹ Palmer H, Graham G, Williams and Day R (2010). A risk-based assessment of paracetamol (acetaminophen) combined with caffeine. *Pain Medicine* 11: 951-965.

PANADOL EXTRA (REFORMULATION) contains a disintegrant system which optimises tablet dissolution compared to existing Panadol Extra.

Human pharmacokinetic data demonstrate that paracetamol and caffeine from PANADOL EXTRA (REFORMULATION) showed faster and greater absorption in the first 60 minutes (t_{max} , $AUC_{0-30min}$ and $AUC_{0-60min}$) compared to existing PANADOL EXTRA.

Maximum plasma concentration of paracetamol is reached faster for PANADOL EXTRA (REFORMULATION) compared to existing PANADOL EXTRA in fasted and fed states ($p < 0.01$). PANADOL EXTRA (REFORMULATION) caplets achieved t_{max} in the fasted state in a faster median time of 0.50 hrs versus 0.99 hrs for existing PANADOL EXTRA. After food, PANADOL EXTRA (REFORMULATION) caplets achieved t_{max} in a faster median time of 1.00 hrs versus 1.25 hours for existing PANADOL EXTRA Caplets.

Total extent of absorption of paracetamol from PANADOL EXTRA (REFORMULATION) is equivalent to that from existing PANADOL EXTRA ($AUC_{0-\infty}$ and AUC_{0-t}).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Starch - pregelatinised maize, calcium carbonate, alginic acid, crospovidone, povidone, magnesium stearate, parahydroxybenzoates (sodium methyl, sodium ethyl, sodium propyl), OPADRY complete film coating system YS-1-7003 WHITE, Carnauba wax, and Water – purified.

Contains no sugar, lactose or gluten.

6.2. Incompatibilities

No known incompatibilities

6.3. Shelf life

24 months

6.4. Special Precautions for storage

Store below 25 degrees Celsius. Keep out of reach of children.

6.5. Nature and contents of container

Blister packs of 10, 20, 40 and 80 caplets

6.6. Special precautions for disposal and other handling

No special requirements

7. MEDICINE SCHEDULE

Packs of 20 and under – General sale

Packs of more than 20 – Pharmacy only

8. SPONSOR

GlaxoSmithKline Consumer Healthcare
Level 11, Zurich House
21 Queen Street
Auckland 1010
New Zealand
FREECALL NZ: 0800 540 144

9. DATE OF FIRST APPROVAL

25/05/2000

10. DATE OF REVISION OF THE TEXT

6 December 2019

Summary table of changes

<u>Section changes</u>	<u>Summary of new changes</u>
6.5	Addition of blister pack of 80 caplets.

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