# AUSTRALIAN PRODUCT INFORMATION
# PANADOL EXTRA (PARACETAMOL AND CAFFEINE) TABLETS

## 1 NAME OF THE MEDICINE

Paracetamol and caffeine

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: Paracetamol 500 mg and caffeine 65 mg/tablet

Excipients:

**PANADOL EXTRA SOLUBLE TABLETS**
Each tablet contains:

- 426 mg of sodium per tablet (854 mg of sodium per 2 tablet dose). To be taken into consideration by patients on a controlled sodium diet.
- 50 mg of sorbitol powder (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Saccharin sodium, which may cause allergic reactions.

**PANADOL EXTRA OPTIZORB CAPLETS**
Each caplet contains:

- parahydroxybenzoates (sodium methyl, sodium ethyl, sodium propyl), which may cause allergic reactions.

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

## 3 PHARMACEUTICAL FORM

**PANADOL EXTRA CAPLETS**

White film coated, capsule-shaped tablet (caplet) with flat edges. “PANADOL EXTRA” is embossed on one face of the caplet.

**PANADOL EXTRA SOLUBLE TABLETS**

Flat, white tablets with bevelled edges, packed in a laminate strip. They effervesce vigorously when placed in water and dissolve to give a clear, odourless solution with a slightly sweet taste.

**PANADOL EXTRA OPTIZORB CAPLETS**

White to off-white, oval shaped film coated tablet, 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 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 DOSE AND METHOD OF ADMINISTRATION

**PANADOL EXTRA caplets and PANADOL EXTRA OPTIZORB caplets** are 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) with water. Maximum of 8 caplets in 24 hours. Not recommended in children under the age of 12 years.

**PANADOL EXTRA Soluble tablets** are to be administered orally, with or without food. For Adults and children 12 years and older: 2 soluble tablets every 4 to 6 hours (as required). Maximum of 8 Soluble tablets in 24 hours. Not recommended in children under the age of 12 years. PANADOL EXTRA soluble tablets should be dissolved in at least half a glass of water.

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment. Do not exceed the stated dose. PANADOL EXTRA should not be used with other paracetamol containing products.

Minimum dosing interval: 4 hours.

Maximum daily dose for children 12 years of age to adults: 4000 mg/520 mg (paracetamol/caffeine).

## 4.3 CONTRAINDICATIONS

These products are contraindicated in patients with a previous history of hypersensitivity to paracetamol, caffeine or to any of the excipients.

## 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.

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

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 in children under the age of 12 years.

**Effects on laboratory tests**

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

Cholestyramine reduces the absorption of paracetamol if given within one 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.

Caffeine may increase the elimination of lithium from the body. Concomitant use is therefore not recommended.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

No data available.

### Use in pregnancy – 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.

Paracetamol is excreted in breast milk. 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.

Caffeine in breast milk may potentially have a stimulating effect on breast fed infants but significant toxicity has not been observed.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

## 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 www.tga.gov.au/reporting-problems.

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.

Table 1: Post marketing data

| **Body System** | **Undesirable Effect** | **Frequency** |
|---|---|---|
| **Paracetamol** | | |
| Blood and lymphatic system disorders | Thrombocytopenia | Very rare |
| Immune System disorders | Anaphylaxis<br><br>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<br><br>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.

### 4.9 OVERDOSE

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 Poisons Information Centre should be contacted immediately for advice (call 131 126), or the patient should go to a hospital straight away, even if they feel well, because of the risk of delayed, serious liver damage. See Adverse Effects.

Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardiac arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, anxiety, tremors and convulsions).

For clinically significant symptoms of caffeine overdose to occur, the amount ingested would be associated with serious paracetamol-related liver toxicity.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

**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.

**Clinical trials**

A meta-analysis to determine the analgesic effect of the combined dosage of paracetamol (1,000 mg) and caffeine (130 mg) versus paracetamol (1,000 mg) 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 8[1].

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

[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.

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.

Regular PANADOL EXTRA caplets and Panadol tablets are bioequivalent for $AUC_{0\text{-}10hr}$ and $C_{max}$ for paracetamol. The extent of absorption (AUC) and peak plasma levels ($C_{max}$) of paracetamol were similar for both products. The time to peak plasma level ($t_{max}$) was not significantly different for regular PANADOL EXTRA caplets and Panadol tablets.

For PANADOL EXTRA soluble tablets the $t_{max}$ for both paracetamol and caffeine was reached twice as fast (0.27 h, 0.32 h respectively) compared to regular PANADOL EXTRA caplets (0.67 h, 0.65 h respectively) {$p \leq 0.043$}.

PANADOL EXTRA OPTIZORB caplets contain a disintegrant system which optimises tablet dissolution compared to regular PANADOL EXTRA caplets.

Human pharmacokinetic data demonstrate that paracetamol and caffeine from PANADOL EXTRA OPTIZORB caplets showed faster and greater absorption in the first 60 minutes (Tmax, $AUC_{0\text{-}30min}$ and $AUC_{0\text{-}60min}$) compared to regular PANADOL EXTRA.

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

Total extent of absorption of paracetamol and caffeine from PANADOL EXTRA OPTIZORB caplets is equivalent to that from regular PANADOL EXTRA Caplets ($AUC_{0\text{-}\infty}$ and $AUC_{0\text{-}t}$).

### 5.3 PRECLINICAL SAFETY DATA

#### Genotoxicity

No data available.

#### Carcinogenicity

No data available.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

**PANADOL EXTRA CAPLETS**

Maize starch, Starch – Pregelatinised maize, Povidone, Potassium sorbate, Purified talc, Stearic acid, Croscarmellose sodium, Hypromellose, Glycerol triacetin.

**PANADOL EXTRA SOLUBLE tablets**

Sorbitol, Saccharin sodium, Sodium bicarbonate, Povidone, Sodium lauryl sulphate, Dimethicone 350, Citric acid (anhydrous), Sodium carbonate (anhydrous).

**PANADOL EXTRA OPTIZORB caplets**

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, Water – purified.

Contains no sugar, lactose or gluten.

## 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 below 25°C.

## 6.5 NATURE AND CONTENTS OF CONTAINER

PANADOL EXTRA CAPLETS
Packs of 10, 18, 36, 64 and 72 caplets.

PANADOL EXTRA SOLUBLE TABLETS
Packs of 24 soluble tablets.

PANADOL EXTRA OPTIZORB CAPLETS
Packs of 10, 20 and 40 caplets.

Not all pack sizes may be marketed.

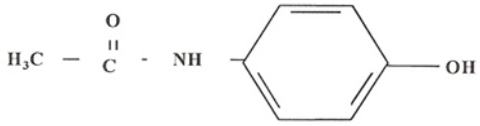
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

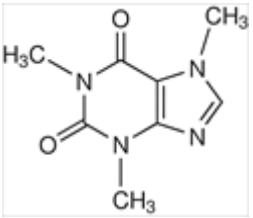
### 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**

Paracetamol



Caffeine



**CAS number**

Paracetamol 103-90-2

Caffeine 58-08-2

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Packs of 10 tablets and 20 tablets - Unscheduled

Packs larger than 20 tablets - S2, Pharmacy Medicine

## 8 SPONSOR

GlaxoSmithKline Consumer Healthcare Australia
82 Hughes Avenue
Ermington
NSW 2115

Telephone: 02 9684 0888
Website: www.gsk.com.au

## 9 DATE OF FIRST APPROVAL

PANADOL EXTRA CAPLETS
(AUST R 166030) 13 October 2009

PANADOL EXTRA SOLUBLE TABLETS
(AUST R 199774) 6 August 2012

PANADOL EXTRA OPTIZORB CAPLETS
(AUST R 203990) 13 December 2012

## 10 DATE OF REVISION

9 April 2018

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| **All** | Reformatted Product Information to new form. |
| **4.2** | Addition of minimum dosing interval, maximum daily dose and use for shortest duration of treatment. |
| **4.4** | Addition of statements relating to liver/kidney impairment and allergic reactions. |
| **4.5** | Additional statement relating to concomitant use of lithium. |
| **4.6** | Addition of statement regarding stimulating effect of caffeine. |
| **4.9** | Additional statements on caffeine overdose. |