DESCRIPTION
Active Ingredients: Paracetamol 500 mg and Caffeine 65mg per tablet.

Excipients: Maize starch
Starch - Pregelatinised maize
Povidone
Potassium sorbate
Purified talc
Stearic Acid
Croscarmellose sodium
Hypermellose
Glycerol triacetin

Contains no sugar, lactose or gluten.

PHARMACOLOGY
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.

Pharmacodynamics
A meta-analysis to determine the analgesic effect of the 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.

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.

**Pharmacokinetics**

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.

PANADOL EXTRA and PANADOL tablets are bioequivalent for \( \text{AUC}_{0-10\text{hr}} \) and \( \text{C}_{\text{max}} \) for paracetamol. The extent of absorption (AUC) and peak plasma levels (\( \text{C}_{\text{max}} \)) of paracetamol were similar for PANADOL EXTRA and PANADOL tablets. The time to peak plasma level (\( t_{\text{max}} \)) was not significantly different.

**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.

**CONTRAINDICATIONS**

PANADOL EXTRA is contraindicated in patients with hypersensitivity to paracetamol, caffeine or to any of the excipients.
PRECAUTIONS
PANADOL EXTRA should be administered with caution to patients with hepatic or renal dysfunction.

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 or other direct or indirect harmful effects on the fetus having been observed.

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.

No definite conclusions can be drawn from available human data. However short-term intake of caffeine from PANADOL EXTRA is comparable to the normal daily intake from common food and drink.

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.

Pregnant mothers should be advised to moderate caffeine intake during pregnancy.

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.

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

Effects on ability to drive and use machinery
PANADOL EXTRA tablets have no influence on the ability to drive or use machines.
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.

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

Caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isozyme 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.

ADVERSE REACTIONS
Reports of adverse reactions are rare. The following adverse reactions have been reported for which a possible causal relationship with paracetamol/caffeine has been established.

Paracetamol
Skin and subcutaneous tissue disorders: very rare (<1/10,000) dermatitis allergic.*

*C hypersensitivity reactions including skin rashes and angioedema have been reported very rarely with paracetamol.

Caffeine
Psychiatric Disorders: very rare (<1/10,000) insomnia and restlessness.

DOSAGE AND ADMINISTRATION
PANADOL EXTRA 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.

Do not exceed the stated dose. PANADOL EXTRA should not be used with other paracetamol containing products.
OVERDOSAGE
Paracetamol overdose may cause liver failure, if left untreated.

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 Reactions.

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

POISONS SCHEDULE
S2 Pharmacy Medicine

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

PRESENTATION
White film coated, capsule-shaped tablet (Caplet) with flat edges. “PANADOL EXTRA” is embossed on one face of the caplet. Packs of 18 and 36 Caplets.

SPONSOR
GlaxoSmithKline Consumer Healthcare
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