

Prescribing Information/Insert

PANADOL EXTRA™

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains paracetamol 500 mg and caffeine 65 mg.

Excipients

Pregelatinised Maize starch, Maize starch, Povidone K 25, Potassium sorbate, Purified Talc (Irradiated), stearic acid, Croscarmellose sodium.

CLINICAL INFORMATION

Indications

Contains paracetamol, which is an analgesic and antipyretic, and caffeine, an adjuvant to the analgesic effect of paracetamol.

a) Treatment of mild to moderate pain and relief of fever including:

- Headache
- Migraine
- Muscle ache.
- Dysmenorrhoea.
- Sore throat
- Musculoskeletal pain.
- Fever and pain after vaccination.
- Pain after dental procedures / tooth extraction
- Toothache.
- Pain of osteoarthritis.

b) For Colds and Flu:

For the relief of symptoms of the common cold and influenza for example headache, fever, sore throat, muscular aches and pains reduced alertness and drowsiness.

Dosage and Administration

Adults (including the elderly) and children aged 12 years and over:

Oral administration only.

500 mg paracetamol/65 mg caffeine to 1000 mg paracetamol/130 mg caffeine (1 or 2 tablets) every 4 to 6 hours as required.

Maximum daily dose: 4000 mg/520 mg (paracetamol/caffeine). Do not exceed the stated dose. The lowest dose necessary to achieve efficacy should be used.

Minimum dosing interval: 4 hours

Populations

Children

Paracetamol-caffeine is not recommended for children under the age of 12 years.

Renal Impairment

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 and caffeine products in patients with renal impairment are primarily a consequence of the paracetamol content of the drug. (*see Warnings and Precautions*).

Hepatic Impairment

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 and caffeine products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drugs. (*see Warnings and Precautions*).

Contraindications

This product is contraindicated in patients with a previous history of hypersensitivity to paracetamol (caffeine or excipients)

Warnings and Precautions

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 can lead to liver transplant or 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 or are chronic heavy users of alcohol. In patients with glutathione depleted states such as sepsis, the use of paracetamol may increase the risk of metabolic acidosis. If symptoms persist, medical advice must be sought. (If cold and flu symptoms persist for longer than 7 days, medical advice must be sought*). Excessive intake of

caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product. Keep out of sight and reach of children.

Interactions

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.

Pregnancy and Lactation

Fertility

No relevant data available.

Pregnancy

Paracetamol: Human and animal studies with paracetamol have not identified any risk to pregnancy or embryo-foetal development

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

Lactation

Paracetamol and caffeine are excreted in breast milk.

Paracetamol: Human studies with paracetamol at the recommended doses have not identified any risk to lactation or the breast-fed offspring.

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

Ability to perform tasks that require judgement, motor or cognitive skills

No significant effect.

Adverse Reactions

Clinical Trial Data

Adverse events from historical clinical trial data are both infrequent and from small patient exposure.

Post Marketing Data

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 ($\geq 1/10,000$, $< 1/1000$), 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
Paracetamol		
Blood and lymphatic system disorders	<i>Thrombocytopenia</i>	Very rare
Immune System disorders	<i>Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes, angiodema, Stevens Johnson syndrome.</i>	Very rare
Respiratory, thoracic and mediastinal disorders	<i>Bronchospasm in patients sensitive to aspirin and other NSAIDs.</i>	Very rare
Hepatobiliary disorders	<i>Hepatic dysfunction</i>	Very rare
Caffeine		
Central Nervous System	<i>Nervousness, Dizziness</i>	Very rare

When the recommended paracetamol-caffeine 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.

Overdosage

Paracetamol Symptoms and Signs

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

Treatment

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

Administration of N-acetylcysteine or methionine may be required.

Caffeine Symptoms and Signs

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

It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity.

Treatment

No specific antidote is available, but supportive measures such as beta adrenergic antagonists to reverse the cardiotoxic effects may be used.

Clinical Pharmacology

ATC code: N02B E01

Pharmacotherapeutic group: Anilides

Mechanism of Action

Paracetamol is an analgesic and antipyretic. Its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system

Pharmacodynamic Effects

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

Caffeine acts as an analgesic adjuvant which enhances the efficacy of paracetamol. Clinical data have demonstrated that paracetamol-caffeine provides superior pain relief compared to standard paracetamol tablets ($p \leq 0.05$).

Pharmacokinetics

Paracetamol

Absorption: Paracetamol is rapidly absorbed from the gastrointestinal tract and is distributed into most body tissues.

Distribution: Binding to the plasma proteins is minimal at therapeutic concentrations.

Metabolism and Elimination:

Paracetamol is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate metabolites - less than 5% is excreted as unmodified paracetamol. The mean plasma half life after oral administration is about 2.3 hours.

Caffeine

Absorption: Caffeine is rapidly absorbed from the gastrointestinal tract.

Distribution: Caffeine is widely distributed throughout the body.

Metabolism and Elimination:

Caffeine is almost completely metabolised in the liver by oxidation and demethylation to various xanthine derivatives, which are excreted in the urine. The mean plasma half life after oral administration is about 4.9 hours..

Special Patient Populations

See *Dosage and Administration*.

Clinical Studies

Two large, randomised, double-blind crossover studies assessing the efficacy of paracetamol and caffeine in tension headache have been reported, in which paracetamol 1000 mg/caffeine 130 mg was compared with paracetamol 1000 mg and placebo. Pooled data from both studies demonstrated statistically significant superior cumulative pain relief values, maximum pain relief and cumulative sums of pain intensity differences over 6 hours for paracetamol/caffeine compared with paracetamol and placebo ($p < 0.001$).

In a third cross-over study patients received a single dose of either paracetamol/caffeine, paracetamol or aspirin (doses not stated) for headache, followed four hours later by a further (different) second dose of medication if required. Following the first dose of treatment,

paracetamol/caffeine was superior in providing pain relief compared with paracetamol or aspirin. Data for the second dose of treatment cannot be interpreted as any carry-over effect was not taken into account. In a study of similar design in post-operative pain, paracetamol/caffeine was shown to be superior to paracetamol and aspirin following a single dose.

Two studies in post-surgical dental pain assessed the efficacy of paracetamol/caffeine compared with paracetamol, placebo and other analgesics. The paracetamol/caffeine combination was superior to paracetamol, but differences did not reach statistical significance, and was also superior to placebo ($p < 0.05$).

Data from three studies in post-partum pain demonstrated superior pain relief with paracetamol/caffeine compared with paracetamol, however these findings were not statistically significant in all studies.

An induced pain model (stimulation of the nasal mucosa with gaseous CO₂ and dry air) has examined the analgesic effects of paracetamol 1000 mg plus caffeine 130 mg versus the individual components given alone and versus placebo. Analgesic effects were assessed by means of cortical evoked potentials and pain ratings.

Paracetamol plus caffeine demonstrated an enhanced analgesic effect throughout the entire observation period of 190 minutes which was not the case for either paracetamol or caffeine. This induced pain model has shown that caffeine enhances and prolongs the analgesic activity of paracetamol. These data are supportive of the analgesic efficacy of the combination in clinical pain conditions.

A review by Laska analysed the data from 30 clinical trials, including six which assessed the efficacy of several doses of paracetamol/caffeine and paracetamol. A dose/effect curve was constructed and an estimation of relative potency for paracetamol/caffeine compared with paracetamol of 1.37 ($p < 0.05$) was made. This indicates the factor by which paracetamol dose would have to be increased in order to obtain the same analgesic effect as the combination.

A series of three studies by Lipton et al demonstrated the efficacy of a combination of paracetamol 250 mg, aspirin 250 mg and caffeine 65 mg at a two tablet dose in alleviating headache pain. Study design, patient population and outcome measures were similar to the study by Lipton et al which compared paracetamol 1 g with placebo. Efficacy measures were similar for both active and placebo treatment groups across the studies and can be regarded as supportive of the efficacy of the combination.

Cognitive impairment (e.g., lack of alertness, difficulty concentrating) associated with cold and 'flu can be improved by treatment with caffeine, and a combination of paracetamol and caffeine. GSK 2011 was a cross over study to evaluate the effect of a paracetamol 1000 mg/caffeine 130 mg combination versus paracetamol 1000 mg alone in improvement in alertness and performance assessment in subjects suffering from the common cold. Cognitive functioning was significantly superior in favour of paracetamol and caffeine at 30 and 60 minutes post dose. GSK 2013 was a parallel group, study, each subject received a single dose of either: paracetamol 1000 mg /caffeine 130 mg; paracetamol 1000 mg; paracetamol 500 mg /caffeine 65 mg; or paracetamol 500 mg.

Measures of cognitive function were significantly superior at 60 minutes post-dose, in favour of the 1000mg paracetamol + 130mg caffeine versus v 1000mg paracetamol alone. Effects of 500 mg paracetamol + 65 mg caffeine compared to 500 mg paracetamol alone did not show consistent differences.

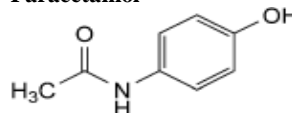
NON-CLINICAL INFORMATION

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

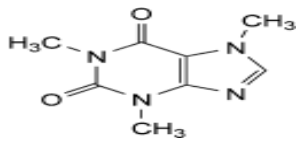
PHARMACEUTICAL INFORMATION

Chemical Structure

Paracetamol



Caffeine

**Shelf-Life**

24 months.

Storage: Store below 30°C.

Nature and Content of Container

20 X 10 Tablets in Alu-PVC blisters.

Incompatibilities

Not Applicable

Use and Handling

No special requirements

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Manufactured by

GlaxoSmithKline Bangladesh Limited,
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