Prescribing Information/Insert

PARAPYROL™

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablet: Each tablet contains paracetamol 500 mg.
Suspension: Each 5 ml contains paracetamol 120 mg.

Excipients

Tablet: Pregelatinised Maize Starch (Amigel), Maize Starch, Potassium Sorbate, Stearic Acid, Powder.
Suspension: Sucrose, Sorbitol Solution 70% w/w (Noncrystallising), Nipagin M, Xanthan Gum, Erythrosine E127 CI 45430, Strawberry Flavour, purified water.

CLINICAL INFORMATION

Indications

Paracetamol is an analgesic and an antipyretic.
a) Treatment of mild-to-moderate pain including:

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

b) Relief of fever.

Dosage and Administration

Tablet
Adults (including the elderly) and children aged 12 years and over:
Oral administration only.
500mg to 1g paracetamol, taken every 4 to 6 hours as required.
Maximum daily dose: 4000 mg. Do not exceed the stated dose
Minimum dosing interval: 4 hours
Children, 6 to 11 years:
500mg tablets: 250 -500mg every 4 to 6 hours as required.
1g tablet: Not recommended for children under the age of 12 years.
Maximum daily dose: 60mg/kg presented in divided doses of 10- 15 mg/kg throughout the 24 hour period
No more than four doses in any 24 hour period.
Maximum duration of continued use without medical advice: 3 days.
Children under 6 years:
Not recommended for children under the age of 6 years
Suspension
Oral administration only.
Children aged 3 months and above: Maximum daily dose: 60mg/kg presented in divided doses of 10- 15 mg/kg throughout the 24 hour period. Do not exceed the stated dose. Should not be used with other paracetamol containing products. No more than four doses in any 24 hour period.
Minimum dosing interval: 4 hours.
Maximum duration of continued use without medical advice: 3 days
Children aged 2 to 3 months: A single dose of 10-15 mg/kg for symptomatic relief of reaction due to vaccination. Medical advice should be sought if pyrexia persists after a second dose. For other interactions, use only under medical advice.
Populations
Children
Tablets: See Dosage and Administration. Not recommended for children under the age of 6 years.
Renal Impairment
Patients who have been diagnosed with kidney impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol 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 impairment must seek medical advice before taking this medication. The restrictions related to the use of paracetamol products in patients with hepatic impairment are primarily a consequence of the paracetamol content of the drug (*see Warnings and Precautions*).

Contraindications

Paracetamol is contraindicated in patients with a previous history of hypersensitivity to paracetamol 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.

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
Human and animal studies with paracetamol have not identified any risk to pregnancy or embryo-foetal development
Lactation
Human studies with paracetamol have not identified any risk to lactation or the breast-fed offspring. Paracetamol crosses the placental barrier and is excreted in breast milk.

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

Unlikely to cause an effect on ability to drive and use machines.

Adverse Reactions

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/labeled 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
80 (≥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.

Post Marketing Data

Body System	Undesirable effect	Frequency
Blood and lymphatic system disorders	*Thrombocytopaenia*	Very rare
Immune System disorders	*Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes, angiodema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis.*	Very rare
Respiratory, thoracic and mediastinal disorders	*Bronchospasm in patients sensitive to aspirin and other NSAIDs.*	Very rare

Hepatobiliary disorders	*Hepatic dysfunction*	Very rare

Overdosage

Symptoms and Signs

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

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.

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)

Pharmacokinetics

Absorption: Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract.

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

Metabolism: Paracetamol is metabolised in the liver and excreted in the urine mainly as glucuronide and sulphate conjugates.

Elimination: Less than 5% is excreted as unmodified paracetamol.

In addition the following apply to specific formulations:

paracetamol concentrations above the minimum level required for analgesia (>4 mcg/ml) were maintained until up to 6 to 7 hours after administration in fasted subjects and 7 to 8 hours in fed subjects. At steady state it 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 sustained release tablets have the characteristics of a formulation containing sustained release paracetamol. Fluctuations in the peak and trough values for plasma paracetamol concentrations were significantly smaller for sustained release tablets than for standard immediate release paracetamol (mean fluctuation index =0.957 and 1.388, respectively, $p<0.001$). Consequently, sustained release tablets provided more consistent levels of paracetamol. Furthermore, the AUCs at steady state were equivalent indicating that there was no additional accumulation of paracetamol from sustained release tablets compared to standard immediate release paracetamol.

Special Patient Populations

See *Dosage and Administration*.

Clinical Studies

Sore throat

A large study demonstrated significant efficacy of a single 1 g dose of paracetamol tablet in reducing pain intensity and providing pain relief in sore throat over a 6 hour period, compared with placebo. This study used validated measures and differences were clinically relevant.

Headache

Three large, randomised, double-blind studies assessing the efficacy of paracetamol it tension headache have been reported, comparing several doses of paracetamol with other analgesics and placebo. Two studies demonstrated statistically significant superior cumulative pain relief values and cumulative sums of pain intensity differences over 6 hours for paracetamol 1 g compared with placebo. Significant differences compared with placebo were observed from one hour after dosing, although separation of benefit commenced as early as 30 minutes after dosing. The third study demonstrated that paracetamol 1 g gave statistically significant superior pain relief compared to placebo.

Muscle Ache

A randomised, double-blind, placebo-controlled study investigated the effect of treatments including paracetamol (1g) in combination with pseudoephedrine in patients with common cold. General muscular ache was assessed during the study and a significant superiority over placebo ($p<0.05$) was demonstrated for the paracetamol combination.

Migraine

A large parallel group study assessed the efficacy of paracetamol 1 g compared with placebo in a single migraine attack. The paracetamol was significantly superior to placebo at 2 hours post-dose for headache response rate, pain-free rate and for other migraine headache symptoms such as photophobia, phonophobia and functional disability. A large cross-over study assessed the efficacy of paracetamol 1 g compared with dihydroergotamine, paracetamol/dihydroergotamine combination and placebo in 4 consecutive migraine attacks. All active treatments were significantly superior to placebo in reducing intensity of pain at one and 2 hours, and brought a significantly faster abatement of pain. A second crossover study compared paracetamol 900 mg with ibuprofen 400 mg in the treatment of classical migraine. Both treatments significantly reduced severity of pain compared with baseline

Dysmenorrhoea

Two placebo-controlled studies examined paracetamol efficacy in dysmenorrhoea. The first study was part of a pooled analysis which compared paracetamol 1g with naproxen sodium 220 mg and placebo. The design was a randomised, double-blind, single dose, cross-over study in patients with primary dysmenorrhoea of moderate to severe intensity. For paracetamol, maximal pain relief was observed at 2 hours post-dose. Paracetamol showed significant pain relief at 2, 3 and 4 hours after administration versus placebo ($p<0.01$) and numerically superior pain relief at 5, 6 and 7 hours after administration. The second study demonstrated that paracetamol 650 mg was superior to placebo in reducing menstrual pain.

Dental Pain

Six studies in dental pain are reviewed. All were large studies, randomised, group comparative and double-blind in design. All except one were placebo-controlled. The non-placebo controlled study compared 2 doses of paracetamol with codeine 60 mg. One study was performed in pre-operative pain), all others were post-operative assessments. In all studies paracetamol 1 g was shown to be statistically superior to placebo or to codeine 60 mg. In one study effervescent paracetamol was shown to have a faster onset of analgesia than standard paracetamol tablets.

Osteoarthritis

A meta-analysis has of the efficacy of paracetamol in the treatment of osteoarthritis showed that paracetamol was significantly more effective in relieving pain due to osteoarthritis than placebo.

Musculoskeletal pain

A study has been performed in acute and chronic moderately severe musculoskeletal pain (including ligament/bone pain, low back strain, osteoarthritis and 14 other conditions) in 90 patients. Pain was significantly reduced compared with baseline in the paracetamol group, but comparisons with placebo were not performed.

Fever

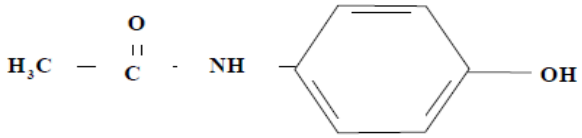
A large, well designed study in adults with fever (associated with upper respiratory tract infection) assessed the efficacy of 500 mg and 1000 mg doses of paracetamol compared with placebo for 6 hours after treatment. Both doses of paracetamol were effective compared to placebo ($p<0.001$) over the 4 hour period and significant temperature reduction for paracetamol persisted for a minimum of 6 hours. Another large, placebo controlled study in adults with fever assessed a single 650 mg dose of paracetamol in an endotoxin-induced model of fever. This study showed a statistically significant and clinically relevant change from baseline in temperature over 8 hours for paracetamol compared with placebo. Other controlled studies have demonstrated the antipyretic efficacy of paracetamol in children.

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



Shelf-Life
Tablet: 36 months
Suspension: 18 months
Storage: Do not store above 30ºC.
Nature and Content of Container
Tablet**:** 50 x 50's polylaminated paper foils strips.
Suspension: 100 ml in amber glass bottle.
Incompatibilities
Not Applicable
Use and Handling
No special requirements

Version Number: PRION Version 6.0
Version Date: 09 February 2016

Manufactured by
GlaxoSmithKline Bangladesh Limited,
Fouzderhat Industrial Area, Chittagong

gsk do more feel better live longer