# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 1000 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1000 mg paracetamol.

## 3 PHARMACEUTICAL FORM

White to off white, caplet shaped tablets, plain on both sides.

### 4.1 Therapeutic indications

For adults and children aged 16 years and over only:

Paracetamol 500 mg Tablets is a mild analgesic and antipyretic, and is recommended for the treatment of most painful and febrile conditions, for example, headache including migraine and tension headaches, toothache, backache, rheumatic and muscle pains, dysmenorrhoea, sore throat, and for relieving the fever, aches and pains of colds and flu. Also recommended for the symptomatic relief of pain due to non-serious arthritis.

## 4.2 Posology and method of administration

*Posology*

Dose depends on the body weight and age; a single dose ranges from 10 to 15 mg/kg body weight to a maximum of 60 mg/kg body weight for total daily dose.

Warning: This medicine contains 1000 mg (1 g) of paracetamol per unit. Patients should be advised not to take two simultaneously.

*Adults, the elderly and children 16 years and over (weighing more than 50 kg):*
Take one tablet every 4-6 hours as required.

**Not recommended for children under 16 years of age.**
The dose should not be repeated more frequently than every 4 hours and not more than 4 doses should be taken in any 24 hours.

The lowest effective dose should be used for the shortest time possible.

Warning: all medicines, including those without prescription, should be taken into account to avoid overdose (see section 4.4).

If pain persists for more than 5 days, fever for more than 3 days, or pain or fever gets worse or other symptoms appear, the clinical situation should be evaluated.

*Renal impairment:*

It is recommended when giving paracetamol to patients with renal impairment, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours unless directed otherwise by a physician. See table:

| Glomerular filtration rate | Dose |
|---|---|
| 10-50 ml/min | 500 mg every 6 hours |
| <10 ml/min | 500 mg every 8 hours |

This product is not suitable for patients with renal insufficiency when a reduced dose is required. More appropriate forms are available for that circumstance.

*Hepatic impairment:*

In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged.

The daily effective dose should not exceed 60 mg/kg/day (up to a maximum 2 g/day) in the following situations:

- Adults weighing less than 50 kg
- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-haemolytic jaundice)
- Dehydration
- Chronic malnutrition
- Chronic alcoholism

*Method of administration*

Oral.

## 4.3 Contraindications

Hypersensitivity to paracetamol or any of the excipients listed in section 6.1

### 4.4 Special warnings and precautions for use

- Care is advised in the administration of paracetamol to patients with renal or hepatic impairment.
- The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.
- Do not exceed the stated dose.
- Patients should be advised to consult their doctor if their headaches become persistent.
- Patients should be advised not to take other paracetamol-containing products concurrently.
- Patients should be advised to consult a doctor if they suffer from non-serious arthritis and need to take painkillers every day.
- Patients should be advised to stop treatment if acute viral hepatitis is diagnosed.
- If symptoms persist consult your doctor.
- Keep out of the reach and sight of children.
- Underlying liver disease increase the risk or paracetamol related liver damage.
- Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.
- Caution should be exercised in patients with glutathione depleted states, as the use of paracetamol may increase the risk of metabolic acidosis (refer also to section 4.9). Use with caution in patients with glutathione depletion due to metabolic deficiencies.
- Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucloxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring, is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

*Pack Label:*
Immediate medical advice should be sought in the event of an overdose, even if you feel well.
Do not take with any other paracetamol-containing products.

*Patient Information Leaflet:*
Immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

### 4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol tablets may be increased by metoclopramide or domperidone and absorption reduced by colestyramine. 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.

Caution should be taken when paracetamol is used concomitantly with flucloxacillin as concurrent intake has been associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risks factors (see section 4.4)

### 4.6 Fertility, pregnancy and lactation

Pregnancy:
A large amount of data on pregnant women indicate neither malformative, nor feto/neonatal toxicity. Epidemiological studies on neurodevelopment in children exposed to paracetamol in utero show inconclusive results. If clinically needed, paracetamol can be used during pregnancy however it should be used at the lowest effective dose for the shortest possible time and at the lowest possible frequency.

Lactation:
After oral administration, paracetamol is excreted into breast milk in small quantities in recommended dosages. No undesirable effects on nursing infants have been reported. Consequently, paracetamol tablets may be used in breast-feeding. Available published data do not contraindicate breastfeeding.

Fertility:
There are no available data on the effect of paracetamol on fertility.

## 4.7 Effects on ability to drive and use machines

None.

### 4.8 Undesirable effects

Adverse events of paracetamol tablets from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by system class and frequency. Due to limited clinical trial data, the frequency of these adverse events is not known (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol tablets are rare and serious reactions are very rare.
The following convention has been utilised for the classification of the undesirable effects: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000), not known (cannot be estimated from available data).
**Post marketing data**

| Body System | Undesirable effect | Frequency |
|---|---|---|
| Blood and lymphatic system disorders | Thrombocytopenia<br>Agranulocytosis | Very Rare |
| Immune system disorders | Anaphylaxis<br>Cutaneous hypersensitivity reactions including skin rashes, angiodema and Very rare cases of serious skin reactions have been reported. | Very Rare |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm* | Very Rare |
| Hepatobiliary disorders | Hepatic dysfunction | Very Rare |
| Metabolism and nutrition disorders | High anion gap metabolic acidosis | Not known |

* There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

Description of selected adverse reactions

High anion gap metabolic acidosis

Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol (see section 4.4). Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at:www.mhra.gov.uk/yellowcard or search MHRA Yellow Card in the Google Play or Apple App store.

## 4.9 Overdose

Liver damage is possible in adults who have taken 10 g or more of paracetamol tablets. Ingestion of 5 g or more of paracetamol tablets may lead to liver damage if the patient has risk factors (see below).

*Risk factors*

If the patient:

a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
b) Regularly consumes ethanol in excess of recommended amounts.
c) Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

*Symptoms*

Symptoms of paracetamol tablets overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema,and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

*Management*

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital. Management of patients who present with serious hepatic dysfunction beyond 24h from ingestion should be discussed with your doctor.

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics and antipyretics, anilides; ATC-code: N02B E01

Paracetamol is an antipyretic analgesic. The mechanism of action is probably similar to that of the aspirin and dependant on the inhibition of prostaglandin synthesis. This inhibition appears, however, to be on a selective basis.

## 5.2 Pharmacokinetic properties

Absorption

The absorption of paracetamol by the oral route is rapid and complete from gastrointestinal tract. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion and the plasma half-life is 1 - 4 hours after therapeutic doses.

Distribution

Paracetamol is distributed rapidly throughout all tissues. Concentration are comparable in blood, saliva and plasma. Protein binding is low. Binding of the drug to plasma proteins is variable; 20 to 30 % may be bound at the concentrations encountered during acute intoxication.

Metabolism

Paracetamol is metabolised mainly in the liver following two major metabolic pathways: glucuronic acid and sulfuric acid conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalysed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination

Elimination is essentially through the urine. 90% - 100% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 60 80%) and sulphate conjugates (20 to 30%). However, practically no paracetamol is excreted unchanged and the bulk is excreted after hepatic conjugation.

Elimination half-life is about 2 hours.

Special patient groups

Renal Insufficiency: In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly Subjects: The capacity for conjugation is not modified.

**5.3 Preclinical safety data**

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Pregelatinised starch
Povidone
Magnesium stearate

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

2 years.

## 6.4 Special precautions for storage

Store in the original package in order to protect from light.

## 6.5 Nature and contents of container

PVC/PVdC/aluminium blisters: 8 & 16 tablets
Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

# 7 MARKETING AUTHORISATION HOLDER

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Units 1-7 Colonial Way, Watford,
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United Kingdom.

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