SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 500mg Tablets
Paracetamol 500mg Caplets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg.

Excipient with known effect: Also contains 0.56mg of Sodium metabisulfite.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, capsule shaped tablet with break-line on one side and plain on the other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of most painful and febrile conditions for example headache including migraine and tension, headaches, neuralgia, toothache, sore throat, period pains, aches and pains. Also recommended for symptomatic relief of rheumatic aches and pains and of influenza, feverishness and feverish colds.

4.2 Posology and method of administration

Posology

Adults, the elderly and children16 years and over:

Take one to two tablets every 4-6 hours, if you need to. Do not take more than 8 tablets in any 24 hours.

Children 10 to 15 years of age:

Take one tablet every 4-6 hours, if you need to. Do not take more than 4 tablets in any 24 hours.

Children under 10 years of age:

Do not give to children under 10 years of age.

Do not take more often than every 4 hours.

Children should not be given Paracetamol for more than 3 days without consulting a doctor.

Method of administration

For oral administration.

4.3. Contra-indications

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

4.4 Special warnings and special precautions for use

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

Patients should be advised that paracetamol may cause severe skin reactions. If a skin reaction such as skin reddening, blisters, or rash occurs, they should stop use and seek medical assistance right away

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.

The concomitant use with other products containing paracetamol may lead to an overdose

Underlying liver disease increases the risk of paracetamol-related liver damage. Patients who have been diagnosed with hepatic or renal impairment must seek medical advice before taking this medication. The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease.

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, dehydrated, 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.

Pack Label:

These words must appear in a prominent position.

"Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor". *This must appear adjacent to either the directions for use or the recommended dosage.*

"Talk to a doctor at once if you take too much of this medicine, even if you feel well";

"Do not take anything else containing paracetamol while taking this medicine".

Patient Information Leaflet:

Talk to a doctor at once if you take too much of this medicine even if you feel well. This is because too much paracetamol can cause delayed, serious liver damage".

Important information regarding the ingredients of this medicine

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

This medicinal product contains sodium metabisulfite which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Colestyramine: The speed of absorption of paracetamol is reduced by colestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone: The absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Warfarin and other anticoagulants: The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

Chloramphenicol: Increased plasma concentration of chloramphenicol.

Flucloxacillin: 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.

Breast-feeding:

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding

4.7. Effects on Ability to Drive and Use Machines

Paracetamol has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following convention has been utilised for the classification of the frequency of adverse reactions: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse reactions 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 MedDRA System Organ Class. As these reactions are reported voluntarily from a population of uncertain size, the

frequency of these reactions is not known but likely to be rare or very rare (<1/1000).

MedDRA SOC	Adverse Reaction Frequency	Frequency
Blood and lymphatic system disorders	Thrombocytopaenia	Very rare
Immune system disorders	Anaphylaxis Cutaneous hypersensitivity reactions including, among others, skin rashes, angioedema, 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

There have been reports of blood dyscrasias including methaemoglobenaemia and agranulocytosis, but these were not necessarily causality related to paracetamol.

MedDRA SOC	Adverse Reaction Frequency	Frequency
Metabolism and nutrition disorders	High anion gap metabolic acidosis	Not known

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 Website:www.mhra.gov.uk/yellowcard or search for the MHRA yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms and Signs

Experience following overdose with paracetamol indicates that the clinical signs of liver injury occur usually after 24 to 48 hours and peak after 4 to 6 days.

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.

There is a risk of poisoning, particularly in elderly subjects, in young adolescents, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal.

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol 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.

Or

b) Regularly consumes ethanol in excess of recommended amounts.

Or

c) Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hrs 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, see BNF overdose section.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hr. 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 hrs after ingestion of paracetamol however, the maximum protective effect is obtained upto 8 hours post ingestion.

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 24 hours from ingestion should be discussed with the NPIS or a liver unit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N02B E01

Pharmacotherapeutic Group: Antipyretic analgesic

Mechanism of Action/ Effect

Analgesic – the mechanism of analgesic action has not been fully determined. Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain- impulse generation.

The peripheral action may also be due to inhibition of prostaglandin synthesis or to inhibition of synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.

Antipyretic- paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat – regulation centre to produce peripheral vasodilation resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves inhibition of prostaglandin synthesis in the hypothalamus.

5.2. Pharmacokinetic Properties

Absorption and Fate

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion. It is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulfate conjugates. Less than 5% is excreted as unchanged paracetamol.

The elimination half-life varies from about 1 to 4 hours. Plasma-protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.
A minor hydroxylated metabolite which is usually produced in very small amounts by mixed-function oxidases in the liver and which is usually detoxified by conjugation with liver glutathione may accumulate following paracetamol overdosage and cause liver damage.

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 Maize Starch
Sodium Metabisulfite
Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3. Shelf life

5 years.

6.4 Special precautions for storage

Blisters: Do not store above 25°C. Store in the original package in order to protect from moisture.

Containers: Do not store above 25°C. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Al/PVC child resistant blisters enclosed in an outer carton.

Pack sizes: 8, 12, 16, 24, 30, 32, 100 tablets

HDPE tablet containers.

OR

Child resistant and adult accessible PP container with HDPE lid

Pack sizes: 16, 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd
Unit 3, Canalside,
Northbridge Road,
Berkhamsted,
Hertfordshire HP4 1EG
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 17907/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation : 13/04/2000
Renewal of the Authorisation: 02/12/2008

10 DATE OF REVISION OF THE TEXT

16/01/2025