# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

PARACETAMOL 500mg CAPSULES

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500mg of paracetamol.

Excipients with known effect: Also contains Methyl parahydroxybenzoate (E218) and Propyl parahydroxybenzoate (E216).

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard gelatin capsule

Red cap, white body, hard gelatin capsule, containing a white free flowing powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For relief of mild to moderate pain including headaches, migraine, aches and pains, symptomatic relief of rheumatic aches and pains and of influenza, muscular and back pain, neuralgia, toothache, sore throat and period pain and to relieve the symptoms of feverishness and colds and flu.

### 4.2 Posology and method of administration

Posology:

Unless otherwise directed by a doctor

**Adults, the elderly and children aged 16 years and over:**

2 capsules up to 4 times a day, as required.

Do not take more frequently than every 4 hours and not more than 8 capsules in any 24 hour period.

**Children aged 12 to 15 years:**

One capsule every 4 – 6 hours when necessary to a maximum of 4 doses in 24 hours

Do not take more than 4 capsules in any 24 hour period

**Children under 12:**
Not recommended for children under 12 years of age.

Method of administration:
For oral administration
Intake of paracetamol with food and drink does not affect the efficacy of the medicinal product.

## 4.3. Contraindications

Hypersensitivity to paracetamol or to 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 hazards of overdose are greater in those with alcoholic liver disease. Paracetamol should be given with care to patients with alcoholic dependence.

Prolonged or frequent use is discouraged. Patients should be advised not to take other Paracetamol containing products concurrently. Taking multiple daily doses in one administration can severely damage the liver; in such case unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In adolescents treated with 60mg/kg daily of Paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised if paracetamol is administered concomitantly with flucloxacillin due to increased risk of high anion gap metabolic acidosis (HAGMA), particularly in patients with severe renal impairment, sepsis, malnutrition and other sources of glutathione deficiency (e.g. chronic alcoholism), as well as those using maximum daily doses of paracetamol. Close monitoring, including measurement of urinary 5-oxoproline, is recommended.

Caution is advised in the administration of Paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatic insufficiency (including Gilbert's syndrome), severe hepatic insufficiency

(child-pugh>9), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, hemolytic anemia, alcohol abuse dehydration and chronic malnutrition (see section 4.2).

The hazards of overdose are greater in those with alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2 grams in such case. Alcohol should not be used during the treatment with Paracetamol.

Paracetamol is well tolerated by the majority of people with asthma. However, a small percentage of aspirin sensitive asthmatics are also sensitive to paracetamol. The likelihood of a reaction to paracetamol increases with a patient's level of sensitivity to aspirin (see also 4.8 Undesirable effects).

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with intravenous busulfan (see section 4.5 Interactions).

Do not exceed the recommended dose.

In the case of high fever, or signs of secondary infection or persistence of symptoms a doctor should be consulted.

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because of the risk of irreversible liver damage (see section 4.9).

If symptoms persist consult your doctor.
Keep out of the sight and reach of children.
Do not take for more than three days unless your doctor agrees.

**The product label will carry the warnings:**
*Do not take anything else containing paracetamol while taking this medicine.*
*Do not take more medicine than the label tells you to. If you do not get better, talk to your doctor.*

**Label**
*Talk to a doctor at once if you take too much of this medicine, even if you feel well.*

**Leaflet or Label/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.*

*Keep this medicine out of the sight and reach of children.*

**Important information regarding the ingredients of this medicine**

Parahydroxybenzoates: This medicine contains Methyl parahydroxybenzoate (E218) and Propyl parahydroxybenzoate (E216), may cause allergic reactions (possibly delayed).

Sodium: This medicine contains less than 1 mmol sodium (23 mg) per capsule , that is to say essentially 'sodium-free'.

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

Hepatotoxic substances may increase the possibility of Paracetamol accumulation and overdose. The risk of hepatotoxicity of paracetamol may be increased by drugs which induce liver microsomal enzymes such as barbiturates, tricyclic antidepressants, and alcohol.

Alcohol: Paracetamol should be given with care to patients with alcohol dependence (see section 4.4).

Analgesics: Diflunisal increases blood concentrations of paracetamol.

Uricosurics: Probenecid can reduce the loss of paracetamol from the body. Probenecid causes an almost 2-fold reduction in clearance of Paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the Paracetamol dose should be considered for concomitant treatment with probenecid.

Salicylamide may prolong the elimination t1/2 of Paracetamol.

Cholestyramine (Anion –exchange resins): The speed of absorption of paracetamol is reduced by cholestyramine. Therefore, the cholestyramine should not be taken within one hour if maximal analgesia is required.

Metoclopramide and Domperidone (motility stimulants): The speed of absorption of paracetamol may be increased by metoclopramide and domperidone. However, concurrent use need not be avoided.

Anticoagulants: Concomitant use of Paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation. 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.

Isoniazid (Antibacterials): Reduction of paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibiting its metabolism in the liver. Isoniazid may increase the risk of hepatotoxicity with therapeutic doses of paracetamol.

Antiepileptics: Carbamazepine, phenobarbital, phenytoin and primidone can reduce the effects of paracetamol clearance, with possible potentiation and increase the risk of its action and/or toxicity, by inhibiting its hepatotoxicity.

Cytotoxic drugs: Paracetamol possibly inhibits metabolism of intravenous busulfan (manufacturer of intravenous busulfan advises caution within 72 ours of paracetamol).

Oral contraceptives: Paracetamol is cleared from the body more quickly in women taking oral contraceptives and the analgesic effects may be reduced.

Lamotrigine: Decrease in the bioavailability of lamotrigine, with possible reduction of its effect, due to possible induction of its metabolism in the liver.

Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxydase-peroxydase.

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, especially in patients with risks factors (see section 4.4)

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosage, but patients should follow the advice of their doctor regarding its use.

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

Following oral administration, Paracetamol is excreted into breast milk in small quantities. To date, no adverse reactions or undesirable effects are

known in association with lactation. Therapeutic doses of Paracetamol can be administered during breast-feeding. 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**

Adverse effects of paracetamol are rare**.**

Gastrointestinal disorders: Cases of acute pancreatitis have been reported. Paracetamol has been widely used and reports of adverse reactions are rare, and are generally associated with overdosage.

Haematological: There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol. Leucopenia, neutropenia and pancytopenia have been reported in association with paracetamol.

Immune system: Hypersensitivity including skin rash, urticaria or angioedema may occur. A small percentage of aspirin-sensitive asthmatics are also sensitive to paracetamol. In such cases, the deterioration in respiratory function induced by paracetamol is milder and shorter than with aspirin (see also 4.4 Special warnings and precautions for use).

Skin and subcutaneous tissue disorders: Very rare cases of serious skin reactions.

Renal and urinary disorders: Nephrotoxic effects are uncommon and have not been reported in association with therapeutic doses, except after prolonged administration.

**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 Store or Apple App Store.

## 4.9. Overdose

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, phenobarbital, 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 depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

***Symptoms***
Symptoms of paracetamol overdose in the first 24 hours are sweating, 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, hypotension, cerebral oedema, coma and death. Prothrombin time may increase with deteriorating liver function. 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 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 24 hours from ingestion should be discussed with the NPIS or a liver unit.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesic and Antipyretic ATC code: N02B E01

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*: Paracetamol is readily absorbed from the gastrointestinal tract.

*Distribution*: Peak plasma concentrations occur about 30 minutes to two hours after ingestion. Paracetamol is distributed into most body tissues. It crosses the placenta and is present in breast milk.

*Metabolism*: It is metabolised in the liver. 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 tissue damage.

*Elimination*: It is excreted in the urine, mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol. The elimination half-

life varies from about 1 to 4 hours. At usual therapeutic concentrations plasma-protein binding is negligible.

### 5.3 Preclinical safety data

There is no pre-clinical data of relevance to the prescriber that are additional to those already included in other sections.

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
Magnesium stearate
Sodium laurilsulfate

*Capsule shell:*
Titanium dioxide E171
Erythrosine E127
Quinoline yellow E104
Patent Blue V E131
Gelatin
Methyl parahydroxybenzoate E218
Propyl parahydroxybenzoate E216

### 6.2 Incompatibilities

None known

### 6.3 Shelf life

4 years

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

### 6.5. Nature and contents of container

Child resistant blister packs comprised of 20µm hard aluminium foil laminated to 15µm rigid PVC, and 250µm PVC. Pack size of 100 capsules.

### 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

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0245

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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