Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol Tablets 500 mg from the makers of Disprin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
White tablets marked with code 293 and partial breaklines on one side and product logo on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A mild analgesic and antipyretic. The tablets are recommended for use in the short-term management of the symptoms of headache, musculoskeletal disorders, menstrual pains, toothache and for relieving the fever, aches and pains of common colds and flu.

Also recommended for the symptomatic relief of mild to moderate pain associated with osteoarthritis.

4.2 Posology and method of administration

Paracetamol should be used at the lowest effective dose for the shortest possible time. The maximum daily dose must not be exceeded.

Posology

Adults, the elderly and children aged 16 years and over: 1 to 2 tablets every 4-6 hours as required. Do not take more than 8 tablets in 24 hours.

Paediatric Population:

Children under 6 years: Not recommended

Aged 6 to 9 years: ½ tablet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours

Aged 10 to 11 years: 1 tablet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours

Aged 12 to 15 years 1 to 1 ½ a tablet every 4-6 hours when necessary to a maximum of 4 doses in 24 hours

Do not give this medicine to your child for more than 3 days without speaking to your doctor or pharmacist.

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 below:

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

Hepatic impairment
In patients with hepatic impairment or Gilbert's Syndrome, the dose should be reduced or the dosing interval prolonged. The daily dose should not exceed 2 g/day unless directed by a physician.

Elderly population:
Experience has indicated that normal adult dosage of paracetamol is usually appropriate. However, in frail, immobile elderly subjects or in elderly patients with renal or hepatic impairment, a reduction in the amount or frequency of dosing may be appropriate (see section 4.4).

The maximum daily dose should not exceed 60 mg/kg/day (up to a maximum of 2 g per day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Method of administration
Oral.

4.3 Contraindications

•Hypersensitivity to paracetamol or any of the other constituents.
•Use in children under 6 years of age.
•Severe hepatocellular insufficiency.

4.4 Special warnings and precautions for use

Patients in whom oxidative liver enzymes have been induced, including alcoholics, those receiving barbiturates and patients who are chronically malnourished may be more sensitive to the toxic effects of paracetamol.

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

Paracetamol should be used in particular caution in patients with

- Hepatocellular insufficiency
- Chronic alcohol abuse
- Severe renal insufficiency (creatinine clearance < 10 ml/min)
- Gilbert's syndrome (constitutional hepatic dysfunction).

With high fever, signs of a secondary infection, or if symptoms persist for more than a few days a doctor must be consulted.

In general, medicines containing paracetamol should only be used for a few days and not in high doses without doctor's or dentist's advice.

Prolonged use of painkillers, especially when several painkilling drugs are taken in combination, may produce permanent kidney damage with the risk of kidney failure (analgesic drug-induced nephropathy).

Abrupt withdrawal after prolonged, highly dosed use of analgesics at variance with their intended use may produce headaches as well as fatigue, muscle pain, nervousness and vegetative symptoms. These withdrawal symptoms abate within a few days. Until then, all painkillers should be avoided and not used again without consulting a doctor.

Paracetamol should be administered with caution under the following circumstances (see section 4.2 where relevant):

- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Elderly

Cases of paracetamol induced hepatotoxicity, including fatal cases, have been reported in patients taking paracetamol at doses within the therapeutic range. These cases were reported in patients with one or more risk factors for hepatotoxicity including low body weight (<50 kg), renal and hepatic impairment, chronic alcoholism, concomitant intake of hepatotoxic drugs, and in acute and chronic malnutrition (low reserves of hepatic glutathione). Paracetamol should be administered with caution to patients with these risk factors. Caution is also advised in patients on concomitant treatment with drugs that induce hepatic enzymes and in conditions which may predispose to glutathione deficiency (see sections 4.2 and 4.9). Doses of paracetamol should be reviewed at clinically appropriate intervals and patients should be monitored for emergence of new risk factors for hepatotoxicity which may warrant dosage adjustment.

If high fever or signs of secondary infection occur or if symptoms persist for longer than 3 days, a physician should be consulted.

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 medical assistance should be sought immediately.

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.

Do not exceed the stated dose.

4.5 Interaction with other medicinal products and other forms of interaction

The gastro-intestinal absorption of paracetamol may be delayed by drugs such as anti-cholinergic agents or opioid analgesics which decrease gastric emptying. The likelihood of toxicity may be increased by the concomitant use of enzyme-inducing agents such as alcohol or anti-epileptic drugs.

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

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.

CYP Inducers: Drugs inducing hepatic cytochrome P-450 isoenzyme 2E1 (CYP2E1) may increase the hepatotoxic potential of paracetamol, whilst also reducing plasma paracetamol levels. For example, anticonvulsants including phenytoin, barbiturates, carbamazepine and alcohol.

Isoniazid: The toxicity of paracetamol may be increased by isoniazid.

Guaifenesin: May increase the rate of absorption of paracetamol

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 risk factors (see section 4.4).

- Use of probenecid inhibits binding of paracetamol to glucoronic acid and thereby leads to reduction of paracetamol clearance of approximately factor 2. In concurrent use with probenecid the paracetamol dose should be reduced.
- Salicylamides may prolong elimination half-life of paracetamol.
- Special caution is necessary in concurrent use of drugs causing enzyme induction as well as potentially hepatotoxic substances.
- Repeated use of paracetamol over several weeks increases the effect of anticoagulants. The occasional use of paracetamol has no significant effect.
- Concomitant use of paracetamol and AZT (zidovudine) increases the risk of neutropenia. This medication and AZT should, therefore, only be used at the same time on doctor's advice.

For oral preparations.

- Concurrent use of drugs that slow gastric emptying, e.g., propantheline, may delay absorption and effect of paracetamol.

Effect of laboratory values

Use of paracetamol may influence uric acid evaluation by phosphorous-wolfram acid and blood glucose level assessment by glucose oxidase peroxidase.

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
Paracetamol is excreted in breast milk. However the level of paracetamol present is not considered to be harmful. During nursing, no adverse effects or side effects have emerged up until now. Therapeutic doses of paracetamol can be administered during nursing.

4.7 Effects on ability to drive and use machines

No information submitted.

4.8 Undesirable effects

Events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System Organ Class and frequency.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10,000, < 1/1000), very rare (< 1/10,000), non 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	Hematopoiesic disorders such as thrombocytopenia, leucopoenia, agranulocytosis, pancytopenia.	Very rare
Immune system disorders	Hypersensitivity reactions from simple skin redness to urticaria, angiodema, dyspnoea, sweating, nausea, drop of blood pressure and anaphylactic shock, which necessitates the immediate discontinuation of therapy. In predisposed patients bronchospasm (analgesic drug-induced asthma). Anaphylaxis Cutaneous hypersensitivity reactions, including skin rashes, angiodema and Stevens Johnson syndrome.	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDSs	Very rare
Hepatobiliary disorders	Increase in liver transaminases Hepatic dysfunction	Rare Very rare

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Risk for intoxication is especially high in elderly patients, small children, patients with liver diseases, chronic alcohol abuse, chronic malnutrition and concurrent use of medicines that lead to enzyme induction. In these cases overdosing may lead to death.

Immediate medical attention (in-hospital if possible) is required in the event of overdose, even if there are no significant early symptoms. There may be no early symptoms following a life threatening overdose. Ingestion of more than 12 g paracetamol (24 standard 500 mg tablets) or more than 150 mg paracetamol per kg bodyweight (9g paracetamol in a 60 kg individual), whichever is the smaller, can cause severe liver damage. An overdose with 6 g or more of paracetamol in a single adult dose or of 140 mg/Kg body weight in children leads to liver necrosis, which could lead to a totally irreversible necrosis and later to hepatocellular insufficiency, metabolic acidosis and encephalopathy. These again could lead to coma, also with death as a result. At the same time, elevated concentrations of transaminases (AST, ALT), lactate dehydrogenase and of bilrubin in combination with an increased thromboplastin time were observed, which can occur after 12-48 hours of use. Clinical symptoms of liver damage become apparent after 2 days and reach a peak after 4-6 days. Acute renal failure and necrosis of the renal tubules can occur, even if there are no serious liver damages. Other not liver-related symptoms that were observed after a paracetamol overdose are myocardial anomalies and pancreatitis.

Intravenous N-acetylcysteine (NAC) is effective when initiated within 8 hours of the overdose. Efficacy declines progressively after this time, but NAC may provide some benefit up to and possibly beyond 24 hours. Oral methionine is also effective provided that it is given within 10 to 12 hours of the overdose. Activated charcoal should be considered if the dose of paracetamol ingested exceeds 12 g or 150 mg/kg, which ever is the smaller, and the procedure can be undertaken within 1 hour of the overdose. Dialysis may reduce the plasma concentration of paracetamol. Evaluation of the plasma concentration of paracetamol is advised. There is little evidence that undertaking gastric lavage will be of benefit to a patient in whom paracetamol is known to have been the only substance ingested.

Symptoms of paracetamol overdose in the first 24 hours may include pallor, nausea, vomiting, anorexia and abdominal pain; followed by a subjective improvement in overall well-being, although mild abdominal pain remains as indication of liver damage. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, coma and death. Also CNS stimulation and delirium may occur initially, followed by CNS

depression, stupor, hypothermia, rapid shallow breathing, hypotension and circulatory failure. Shock may also develop as well as seizures and coma.

Liver damage results when excess quantities of a toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested) becomes irreversibly bound to liver tissue.

Paracetamol overdose can result in liver damage which may be fatal.

Overdose of paracetamol can cause liver cell necrosis likely to induce complete and irreversible necrosis, resulting in hepatocellular insufficiency, metabolic acidosis and encephalopathy which may lead to coma and death. Simultaneously, increased levels of hepatic transaminases (AST, ALT), lactate dehydrogenase and bilirubin are observed together with increased prothrombin levels that may appear 12 to 48 hours after administration.

Liver damage is likely in patients who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity:
Risk factors include;

- Patients with liver disease
- Elderly patients
- Young children
- Patients receiving long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
- Patients who regularly consume ethanol in excess of recommended amounts
- Patients with glutathione depletion e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia
- Patients taking isoniazid

Acute renal failure with acute tubular necrosis may also develop.

Cardiac arrhythmias and pancreatitis have also been reported.

Emergency Procedure:

Immediate transfer to hospital.

Blood sampling to determine initial paracetamol plasma concentration. In the case of a single acute overdose, paracetamol plasma concentration should be measured 4 hours post ingestion. Administration of activated charcoal should be considered if the overdose of paracetamol has been ingested within the previous hour.

The antidote N-acetylcysteine, should be administered as soon as possible in accordance with national treatment guidelines. Symptomatic treatment should be implemented.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics and antipyretics. Anilides.

ATC Code: N02B E01.

Paracetamol has analgesic and antipyretic actions.

5.2 Pharmacokinetic properties

Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 15 minutes to 2 hours after ingestion. It is metabolised in the liver and 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 1.5 to 3 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 oxidase 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

Maize starch
Pregelatinised Maize Starch
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Keep blisters in the outer carton.

6.5 Nature and contents of container

Blister packs consisting of 250µm clear PVC and 20µm hard temper aluminium foil.

Pack sizes: 12, 24 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Reckitt Benckiser Ireland Ltd
7 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0979/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

September 2024