Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paracetamol 500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg.

Excipients	Propylparahydroxybenzoate (E216)	0.625 mg
	Sodium methylparahydroxybenzoate (E219)	0.225 mg
	Sodium ethylparahydroxybenzoate (E215)	0.045 mg
	Sodium propylparahydroxybenzoate (E217)	0.030 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, circular, flat, beveled-edge tablets with a breakline on one side.

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

Adults:

The usual dose is 1-2 tablets 3 to 4 times daily. A maximum dose of 8 tablets daily should not be exceeded.

Children

Aged 6 to 12 years: ½ to 1 tablet 3 to 4 times daily. Maximum dose of 4 tablets should not be exceeded.

Children under 6 years: Not recommended.

Route of administration

Oral.

4.3 Contraindications

- Hypersensitivity to paracetamol or any of the other constituents.
- Use in children under 6 years of age.
- Severe hepatic insufficiency (Child-Pugh > 9).

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.

The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease.

Contains parahydroxybenzoates which may cause allergic reactions (possibly delayed).

Special labelling requirements:

1. Prolonged use without medical supervision could be harmful.
2. Do not exceed the stated dose.
3. Consult your doctor if symptoms persist.
4. This product should only be used when clearly necessary.
5. Keep out of reach of children.
6. Patients should be advised not to take other paracetamol-containing products concurrently. Exceeding the recommended dose can lead to severe liver damage (See section 4.9, Overdose).

Paracetamol should be used in particular caution in patients with

- Hepatic insufficiency (Child-Pugh <9)
- 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 use of high dosages of analgesics at variance with their intended application 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, but should be used with caution if use is necessary.

4.5 Interaction with other medicinal products and other forms of interaction

- Use of probenecid inhibits binding of paracetamol to glucuronic acid and thereby leads to reduction of paracetamol clearance by approximately a factor of 2. In concurrent use with probenecid the paracetamol dose should be reduced.

- Special caution is necessary in concurrent use of drugs causing enzyme induction as well as potentially hepatotoxic substances (see 4.9 overdose).

- Repeated use of paracetamol over several weeks increased the anticoagulant effect of warfarin and other coumarins. The occasion 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.

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

paracetamol.

- Concomitant use of drugs that accelerate gastric emptying e.g. metoclopramide or domperidone will speed the absorption and effect of paracetamol.

- Cholestyramine reduces the absorption of paracetamol.

4.6 Fertility, pregnancy and lactation

There is epidemiological evidence of the safety of paracetamol in human pregnancy. Paracetamol is the mild analgesic of choice during pregnancy. However, as with all drugs, caution should be exercised in its use during the first trimester.

Paracetamol should not be used during pregnancy for prolonged periods of time, in high dosage or in combination with other drugs, because safety in these circumstances has not been established.

Lactation
Paracetamol is excreted in breast milk. However the level of paracetamol present is not considered to be harmful. During nursing, no adverse effects have emerged to date.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Adverse events 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), not 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	Haematopoietic disorders such as thrombocytopenia, leucopenia, agranulocytosis, and pancytopenia.	Very rare
Immune system disorders	Hypersensitivity reactions from simple skin redness to urticaria, angiodema, Stevens Johnson syndrome, dyspnoea, sweating, nausea, drop of blood pressure and anaphylactic shock, which necessitates the immediate discontinuation of therapy. Anaphylaxis	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

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.

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. 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. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics and antipyretics. Anilides.

ATC Code: N02B E01.

Paracetamol has analgesic and antipyretic actions but it has no useful anti-inflammatory properties. It is only a weak inhibitor or prostaglandin biosynthesis, although there is some evidence to suggest that it may be more effective against enzymes in the central nervous system than those in the periphery. This fact may partly account for its well documented ability to reduce fever and to induce analgesia, effects that involve actions on neural tissue. Single or repeated doses of paracetamol have no effect on the cardiovascular and respiratory systems. Acid-base changes do not occur. Paracetamol does not produce the gastric irritation, erosion or bleeding that may occur with salicylates. It has only a weak effect upon platelets and no effect on bleeding time or the excretion of uric acid.

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 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

No information submitted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Maize starch
Methylcellulose 450 mPa.s
Propyl parahydroxybenzoate (E216)
Sodium starch glycolate (Type A)
Magnesium stearate
Stearic acid 50
Nipasept sodium consisting of:
Sodium methylparahydroxybenzoate (E219)
Sodium ethylparahydroxybenzoate (E215)
Sodium propylparahydroxybenzoate (E217)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Tubs

Do not store above 25°C.
Keep the container tightly closed.
Store in the original package.

Blister

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

6.5 Nature and contents of container

(i) Blister strip consisting of clear PVC and 20µm hard aluminium foil contained in a carton.

Pack sizes: 12 and 24 tablets

(ii) PP containers with child-resistant lids.

Pack sizes: 24, 30, 50 and 100 tablets.

(iii) Polypropylene tubes with polyethylene caps.

Pack sizes: 250, 500 and 1,000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Limited
Waterford Road
Clonmel
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 126/65/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 1986

Date of last renewal: 02 July 2006

10 DATE OF REVISION OF THE TEXT

December 2010