Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paralief 500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White tablets marked with the code 293 and partial breaklines on one side and the Clonmel 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 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

Posology

Adults and adolescents over 16 years of age:
The usual dose is one to two tablets 3 to 4 times daily. A maximum dose of eight tablets daily should not be exceeded.

Paediatric Population

For children 6 to 9 years of age:
Give half a tablet with a drink of water, every 4 to 6 hours as required. A maximum dose of two tablets daily should not be exceeded.

For children 10 to 11 years of age:
Give one tablet with a drink of water, every 4 to 6 hours as required. A maximum dose of four tablets daily should not be exceeded.

For adolescents 12 to 15 years of age:
Give one to one and a half tablets with a drink of water, every 4 to 6 hours as required. A maximum of six tablets daily should not be exceeded.

Children under 6 years:
Not recommended.

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:

Adults:

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.

The elderly:
Experience has indicated that normal adult dosage 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. 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 50 kg
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

Method of administration

Oral.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Use in children under 6 years of age.

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.

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; in such case medical assistance should be sought immediately (See section 4.9, Overdose).

Paracetamol should be used with particular caution in patients with
- Hepatic impairment
- Chronic alcohol abuse
- Renal impairment (GFR ≤50 ml/min)
- Gilbert's syndrome (constitutional hepatic dysfunction).
- Concomitant treatment with medicinal products affecting hepatic function
- Glucose-6-phosphate dehydrogenase deficiency
- Haemolytic anaemia
- Glutathione deficiency
- Dehydration
- Chronic malnutrition

- Weight less than 50 kg
- Elderly

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).

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.

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 interactions

- 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.

- 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
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. 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

Paralief has no or negligible influence on the ability to drive and use machines.

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. Very rare cases of serious skin reactions have been reported 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

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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

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

Symptoms generally appear within the first 24 hours and may comprise: nausea, vomiting, anorexia, pallor, and abdominal pain, or patients may be asymptomatic.

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

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 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

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

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

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

6.5 Nature and contents of container

Blister packs consisting of 250µm clear PVC and 20µm hard temper aluminium foil in pack sizes of 12 and 24 tablets.

Polypropylene tubes with polyethylene caps.

OTC packs: 12 and 24 tablets.

Dispensing packs: 30, 36, 48, 50, 100, 250, 500 and 1000 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 Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/020/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 May 1981

Date of last renewal: 08 May 2006

10 DATE OF REVISION OF THE TEXT

June 2022