Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paralief 500 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 500 mg of paracetamol.

Excipient(s) with known effect
Each capsule contains 108.0 mg sorbitol and 20.0 mg propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, soft.
White opaque colour oval shape soft gelatin capsule containing off white to white colour suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the short-term treatment of headache, toothache, muscle ache, lumbago, fever and pain with flu and colds.

4.2 Posology and method of administration

Posology

Adults and adolescents older than 15 years (> 55 kg body weight)
1 or 2 capsules (500-1,000 mg) at a time, with a maximum of 6 capsules (3,000 mg) within 24 hours.

Adults and adolescents older than 15 years (≤ 55 kg body weight)
The effective daily dose should not exceed 60 mg/kg/day (up to 2 g/day).

Special populations

Renal impairment
In the case of unsatisfactory activity of the kidneys (renal insufficiency), the dose must be reduced:

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

Hepatic impairment
For patients with unsatisfactory activity of the liver (hepatic insufficiency) or Gilbert's syndrome, the dose must be reduced or the administration intervals must be prolonged.
The effective daily dose should not exceed 60 mg/kg/day (up to 2 g/day).

Patients suffering from dehydration, chronic malnutrition or chronic alcoholism
The effective daily dose should not exceed 60 mg/kg/day (up to 2 g/day).

Paediatric population

Children weighing less than 30 kg (approx. below 9 years of age)
Paralief should not be used in children weighing less than 30 kg (approximately below the age of 9 years). For those children other formulations and dosage strengths are available which may be more appropriate.

Children and adolescents weighing between 31 and 55 kg (approx. 9 to 15 years of age)

- Children weighing 31 to 40 kg (approximately 9 to 12 years of age): 1 capsule (500 mg) at a time, with a maximum of 3 to 4 capsules (2,000 mg) within 24 hours.
- Adolescents weighing 41 to 55 kg (approximately 12 to 15 years): 1 capsule (500 mg) at a time, with a maximum of 4 to 6 capsules within 24 hours.

The lower frequency of administration is intended for the youngest children in the relevant age group. For children weighing less than 50 kg (approximately below 12 years of age) the daily dose should not be higher than 60 mg/kg body weight.

Instructions on use

- The administration interval must be at least 4 hours.
- Do not exceed the stated dose on account of the risk of severe hepatic damage (see section 4.4 and 4.9).
- The lowest possible dose that is required to be effective, should be used.

Method of administration
Oral.
Swallow capsule with sufficient water.

Duration of treatment
If the pain lasts for longer than 5 days or fever lasts for longer than 3 days or these symptoms become worse or if other symptoms occur, the treatment must be stopped and a doctor must be consulted.

The administration of high doses of paracetamol for long periods of time should be avoided since it increases the risk of liver damage.

Depending on the recurrence of symptoms (fever and pain), repeated administration is allowed.

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

Long-term or frequent use is not advised.

Long-term use can be harmful except under medical supervision. In young people who are treated with 60 mg/kg/day of paracetamol, combination with another antipyretic is not allowed except where there is a lack of efficacy.

After the long-term use (> 3 months) of analgesics with intake every other day or more frequently, headache can occur or become worse. Headache, which is caused by the excessive use of analgesics (drug-dependent headache), must not be treated by increasing the dose. In these cases, the use of analgesics must be stopped in consultation with a doctor.

The patient should be advised to avoid the simultaneous use of this medicinal product with others containing paracetamol, such as flu or cold medicinal products. If another medicine containing paracetamol is administered, the maximum paracetamol dose of 3,000 mg per day should not be exceeded, taking into account the content of all the medicines used by the patient. An overdose of paracetamol can cause liver failure, which can require a liver transplant or lead to death.

Caution is required in the case of hepatic and renal impairment. Underlying liver disorders increase the risk of paracetamol-related liver damage. Patients diagnosed with impaired liver or kidney function, should seek medical advice before taking this medicinal product.

The taking of several daily doses at once can cause severe damage to the liver. In such cases, a loss of consciousness will not occur. However, immediate medical help must be sought even if the patient feels well because of the risk of irreversible damage to the liver (see section 4.9).

Caution is required when administering paracetamol to patients with moderate to severe renal insufficiency, mild to moderate hepatic insufficiency (incl. Gilbert's syndrome), severe hepatic insufficiency (Child-Pugh > 9), acute hepatitis, the concomitant administration of medicinal products which have an influence on hepatic function, glucose-6-phosphate dehydrogenase deficiency, haemolytic anaemia, alcohol abuse, dehydration and chronic malnutrition.

The risk of an overdose is greater in patients with non-cirrhotic alcoholic liver conditions. Caution is required in the case of chronic alcoholism. The daily dose may not exceed 2 grams in this case. No alcohol may be used during treatment with paracetamol.

In the case of a high fever, symptoms of secondary infection or the persistence of symptoms, it will be necessary to reconsider the treatment.

Caution is required in the case of asthmatic patients who are sensitive to acetylsalicylic acid as mild bronchospasms have been reported as a cross-reaction after the use of paracetamol.

Cases of hepatic impairment or liver failure have been reported in patients with glutathione depletion, such as patients with severe malnutrition, anorexia or a low body mass index, or patients who chronically consume too much alcohol. In patients with a condition of glutathione depletion such as sepsis, the use of paracetamol may increase the risk of metabolic acidosis (see section 4.9).

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.

Effect on laboratory tests
Paracetamol can have an influence on the urine test with wolfram phosphoric acid as well as the blood sugar test with glucose oxidase peroxidase.

Excipients
This medicinal product contains 108.0 mg sorbitol in each capsule. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicinal product contains 20.0 mg propylene glycol in each capsule.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol is metabolised in the liver and can consequently enter into interactions with other medicinal products which follow the same metabolic route or which are able to inhibit or induce the route. In the case of chronic alcohol abuse and the use of drugs, which induce hepatic enzymes such as barbiturates and tricyclic antidepressants, an overdose of paracetamol can take a more severe course as a result of the increased and more rapid formation of toxic metabolites.

Caution is required with the concomitant intake of enzyme-inducing drugs (see section 4.9 Overdose).

In the case of concomitant treatment with probenecid, the dose of paracetamol must be reduced as probenecid reduces the clearance of paracetamol by 50 % since it prevents the conjugation of paracetamol with glucuronic.

Paracetamol can cause an increase in the half-life of chloramphenicol.

The rate of absorption of paracetamol can be increased by metoclopramide or domperidone and absorption can be reduced by colestyramine.

The anticoagulatory effect of warfarin and other coumarins can increase during the long-term, regular use of paracetamol with an increase in the risk of bleeding as a result. There is no significant effect with the occasional taking of a dose.

With the concomitant chronic use of paracetamol and zidovudine, neutropenia often occurs, probably as a result of the reduced metabolism of zidovudine because of the competitive prevention of conjugation. Concomitant intake of paracetamol and zidovudine should therefore only take place on medical advice.

Salicylamide can prolong the half-life of paracetamol.

Isoniazid ensures a reduction in the clearance of paracetamol, which possibly increases the activity and/or toxicity of paracetamol by preventing metabolism in the liver.

The concomitant intake of paracetamol with lamotrigine ensures a reduction in the bioavailability of lamotrigine, as a result of which there is possibly a decrease in activity as a result of the possible induction of metabolism in the liver.

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 eliminated in the maternal milk. No adverse effects have been reported in children who are breast-fed. Paralief can be used in therapeutic doses by women who breast-feed.

Fertility
There are no available data on the effect of paracetamol on fertility.

4.7 Effects on ability to drive and use machines

As far as is known, this medicinal product does not have any influence on the ability to drive or the ability to use machines.

4.8 Undesirable effects

Few side effects occur at a therapeutic dose.

In this section, frequencies of undesirable effects are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Rare: Agranulocytosis (after long-term use), thrombocytopenia, thrombocytopenic purpura, leukopenia, haemolytic anaemia.
Very rare: Pancytopenia.

Immune system disorders
Rare: Allergies (exclusive of angioedema).
Very rare: Hypersensitivity reaction (angioedema, breathing difficulties, perspiration, nausea, hypotension, shock, anaphylaxis), as a result of which treatment has to be stopped.

Metabolism and nutrition disorders
Very rare: Hypoglycaemia.
Not known: High anion gap metabolic acidosis.

Psychiatric disorders
Rare: Depression, confusion, hallucinations.

Nervous system disorders

Rare: Tremor, headache.

Ophthalmological abnormalities
Rare: Visual abnormalities.

Cardiac disorders
Rare: Oedema.

Respiratory, thoracic and mediastinal disorders
Very rare: Bronchospasm in patients who are sensitive to aspirin and other NSAIDs (analgesic asthma).

Gastrointestinal disorders
Rare: Bleeding, abdominal pain, diarrhoea, nausea, vomiting.

Hepatobiliary disorders
Rare: Abnormal hepatic function, hepatic failure, hepatic necrosis, jaundice.
Very rare: Hepatotoxicity.

Quantities of even 6 g of paracetamol can cause liver damage (in children weighing more than 140 mg/kg); larger quantities cause irreversible hepatic necrosis. Liver damage has been reported after the chronic use of 3-4 g of paracetamol per day.

Skin and subcutaneous tissue disorders
Rare: Pruritus, rash, perspiration, purpura, urticaria.
Very rare: Exanthema, severe skin reactions.
Not known: Acute generalised exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), drug- induced dermatosis, Stevens-Johnson syndrome.

Renal and urinary disorders
Very rare: Sterile pyuria (cloudy urine) and renal side effects (severe renal impairment, interstitial nephritis, haematuria and anuresis).

General disorders and administration site conditions
Rare: Dizziness (excluding vertigo), malaise, pyrexia, sedation, a drug interaction, which is not specified in any more detail.

Injury, poisoning and procedural complications
Rare: Overdose and intoxication.

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

4.9 Overdose

There is a risk of intoxication with paracetamol, particularly in elderly people, young children and patients with hepatic disorders, in cases of chronic alcoholism, in patients with chronic malnutrition and in patients who use enzyme-inducing drugs. Overdose can be fatal. Also, see section 5.2.

Symptoms
The symptoms of paracetamol intoxication are nausea, vomiting, anorexia, pallor and abdominal pain and these symptoms usually occur within 24 hours of intake. From an overdose of paracetamol of 140 mg/kg, moderate liver damage can occur as a result of hepatic cytolysis. From 200 mg/kg, severe hepatic damage can occur, resulting in hepatocellular insufficiency,

metabolic acidosis and encephalopathy, which can result in coma and death. Concomitantly, elevated levels of hepatic transaminases (AST and ALT), lactate dehydrogenase and bilirubin have been observed together with lower prothrombin levels, which can occur 12 to 48 hours after administration. Clinical manifestations of hepatic damage are first usually only visible after two days and reach a maximum after 4 to 6 days.

Management
Immediate admission to hospital even if no symptoms of overdose are present.
After an overdose, a sample of blood should be taken as quickly as possible before the start of the treatment in order to establish the paracetamol content.

In the case of a large overdose, which possibly results in severe intoxication, absorption-reducing therapy can be used: gastric lavage if able to be undertaken within 1 hour of intake and administration of activated charcoal.

Treatment includes the administration of the antidote N-acetylcysteine (NAC) or methionine, either intravenously or orally (if so, do not administer any activated charcoal!), where possible before the 10th hour after intake. NAC can however, improve the prognosis even up to 36 hours after intake if the paracetamol concentration is still demonstrable. Further treatment is symptomatic.

Hepatic tests must be performed at the start of the treatment and must be repeated every 24 hours. In most cases, the hepatic transaminases will return to normal within one to two weeks with a complete restoration of hepatic function. In very rare cases, however, liver transplantation can be necessary.

Gastrointestinal symptoms such as burping and nausea can be expected with high doses of sodium bicarbonate. High doses of sodium bicarbonate can also cause hypernatriaemia; the electrolytes must be monitored and the patient must be treated accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: analgesics, anilides
ATC code: N02BE01

Paracetamol has both analgesic as well as antipyretic activity. However, it does not have anti- inflammatory activity. The mechanism of action of paracetamol has so far not been fully explained. The effect appears to be based on inhibition of the enzyme prostaglandin synthetase, but the lack of an anti-inflammatory effect cannot be explained by this. It is possible that the distribution of paracetamol over the body and hence the site of the inhibition of prostaglandin synthetase plays a role. Paracetamol has the advantage that a number of side effects which are characteristic of NSAIDs are completely or largely absent in the case of paracetamol.

Paracetamol is, therefore, a good alternative to NSAIDs for combating pain and fever.
In an acute pain study with paracetamol, there was no difference in the onset of pain relief between fasting and feeding people.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is quickly and almost completely absorbed after oral administration.
The maximum plasma concentration is reached 15 minutes to 1.5 hours after intake. The maximum concentration is reached 30 minutes to 2 hours after the intake of regular paracetamol capsules.

Distribution
The distribution volume of paracetamol is about 1 l/kg of body weight. The amount of plasma protein binding is negligible at therapeutic doses. The concentration in saliva and maternal milk is related to the plasma concentration.

Biotransformation
Paracetamol is conjugated with glucuronic acid (around 60 %), sulphate (around 35 %) and cysteine (around 3 %) in the liver of adults. With the help of cytochrome P-450, a small proportion of paracetamol is converted in the body into a very reactive metabolite, which is normally quickly inactivated by conjugation with glutathione. Overdose can deplete glutathione stocks and thus result in acute hepatic damage.

Elimination
Paracetamol is mainly excreted in the urine. 90 % of the dose taken is excreted via the kidneys within 24 hours, mainly in the form of the glucuronide (60-80 %) and the sulphate conjugate (20-30 %) and with around 5 % unchanged.
The elimination half-life ranges from 1 to 4 hours. In the case of severe renal insufficiency (creatine clearance of less than 10 ml/min), the elimination of paracetamol and its metabolites is delayed. The conjugation capacity is unchanged in the case of elderly people.

5.3 Preclinical safety data

No special requirements.

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

Capsule content
Macrogol 400
Propylene glycol (E 1520)
Silica, colloidal hydrated
Purified water

Capsule shell
Gelatin
Sorbitol liquid (E 420)
Titanium dioxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30 °C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Cardboard box with PVC/PVDC-Al blisters (90 GSM-30 µm) containing 20 soft capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary

E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/020/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th April 2021

10 DATE OF REVISION OF THE TEXT

March 2025