Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paralief 500 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg paracetamol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white coloured, caplet shaped film-coated tablets with flat-edges debossed with "PARA500" on one side and score line on the other side. Approximately, the tablet dimensions are 17.5 mm X 7.3 mm.

The tablet can be divided into two equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term symptomatic treatment of mild to moderate pain and/or fever.

4.2 Posology and method of administration

Posology
Paracetamol is dosed depending on bodyweight and age, usually with 10 to 15 mg/kg bodyweight as a single dose, up to a maximum of 60 mg/kg bodyweight as a total daily dose.

Adults and adolescents 15 years and above (> 55 kg bodyweight)
1 to 2 tablets (500-1000 mg) at a time, up to 6 tablets (3000 mg) per 24 hours.
The simultaneous intake of two tablets should be recommended only if there is insufficient relief with one tablet, or there is higher requirement due to more intense pain.

Paediatric population (children from 6 years of age (> 22 kg bodyweight) and adolescents up to 15 years (< 55 kg bodyweight))

Age group	Recommended Dose	Number of Tablets	Frequency
6-9 years (22-30 kg bodyweight)	250 mg	Half tablet	Every 4-6 hours when necessary to a maximum of 4-6 doses (1000-1500 mg) in 24 hours
9-12 years (30-40 kg bodyweight)	500 mg	One tablet	Every 4-6 hours when necessary to a maximum of 4 doses (1500-2000 mg) in 24 hours
12-15 years (40-55 kg bodyweight)	500 mg	One tablet	Every 4-6 hours when necessary to a maximum of 4-6 doses (2000-3000 mg) in 24 hours

The lower dosing frequency is intended for children in the lower limit of the relevant weight and / or age group.

Direction for use:

- Paracetamol tablet is not suitable for children below 6 years. For children under 6 years other formulations and dosage strengths are available which may be more appropriate.

- The dosing interval should be at least 4 hours.
- Do not use in combination with other paracetamol-containing products.
- The indicated dose should not be exceeded due to risk of serious damage to the liver (see section 4.4 and 4.9).
- The lower frequency of administration is intended for children in the lower limit of the relevant age group.
- Depending on the onset of symptoms (fever and pain) repeated administration is allowed.
- The ingestion of paracetamol with food and drink does not affect the efficacy of the medicinal product.
- In case of renal insufficiency (renal failure), the dose should be reduced and a minimum dosing interval of 6 hours, see table:

Adults

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

- In patients with impaired hepatic or Gilberts syndrome, the dose must be reduced or the dosing interval prolonged.
- The daily effective dose should not exceed 60 mg/kg/day (up to maximum 2 g/day) in the following situations:
- Adults weighing less than 50 kg
- Mild to moderate hepatic insufficiency, Gilbert's syndrome (familial non-haemolytic jaundice)
- Dehydration
- Chronic malnutrition

The administration of high doses of paracetamol for long periods of time should be avoided since it increases the risk of liver damage. Treatment should be as short as possible.
If the pain continues for more than 5 days, the fever for more than 3 days or the pain or fever worsens or other symptoms appear, the clinical situation should be evaluated.

Method of Administration
For oral use only.

The tablet should be swallowed with a large amount of water or, if desired, left to dissolve in plenty of water, which should be stirred well before drinking.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Prolonged or frequent use is discouraged. In general, medicines containing paracetamol should only be used for a few days and not in increased doses without medical or dental advice.

To avoid the risk of overdose, ensure that medicines used at the same time do not contain paracetamol such as flu or cold medicines. If another medicine containing paracetamol is administered, the maximum paracetamol dose of 3 g per day should not be exceeded, taking into account the content of all the medicines used by the patient.

The one-time intake of the total daily dose, multiple daily doses or in the event of overdosage may cause severe damage to the liver; in such cases, immediate medical advice should be sought even if the patient feels well because of the risk of irreversible liver damage (see section 4.9).

In young subjects treated with 60 mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Caution is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment (child-Pugh> 9), mild to moderate hepatic impairment (incl. Syndrome Gilbert), acute hepatitis, concomitant administration of drugs that affect the liver function, glucose-6-phosphatedehyrogenase deficiency, haemolytic anaemia, alcohol abuse, chronic dehydration and malnutrition.

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

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.

In cases of high fever, signs of a secondary infection, or persistence of the symptoms for more than three days, medical advice should be sought.

After prolonged use (> 3 months) of analgesics intake every day or more often, headaches may occur or worsen. Headaches caused by overuse of analgesics (mean-tested headache) should not be handled by increasing the dose. In those cases, the use of analgesics should be taken after consulting a doctor.

In general, the habitual use of analgesics, especially in combination with several analgesic agents, can lead to permanent kidney damage with the risk of kidney failure (analgesic nephropathy).

Caution is advised in asthmatic patient sensitive to acetylsalicylic acid, because light reaction bronchospasm with paracetamol (cross-reaction) has been reported.

Hepatotoxicity at therapeutic dose of paracetamol
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.

Paralief contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The speed of absorption of paracetamol and the onset of action may be increased by metoclopramide or domperidone, or agents that lead to an acceleration of gastric emptying and absorption reduced by cholestyramine and agents that slow down the emptying of the stomach. The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged daily use of paracetamol with increased risk of bleeding. Occasional doses have no significant effect.

Paracetamol is extensively metabolized in the liver and can therefore interact with medicinal products with the same metabolic pathway or induce/inhibit the same metabolic pathway. Chronic use of alcohol or medicinal products which induce liver enzymes like rifampicin, barbiturates, some anti-epileptic drugs (e.g. carbamazepine, phenytoin, phenobarbital, pirimidone) and St. John's Wort can increase the hepatotoxicity of paracetamol as a result of an increased and fast formation of toxic metabolites. Caution is therefore necessary with concomitant use of enzyme-inducing drugs as well as for potentially hepatotoxic substances.

Paracetamol increases the plasma concentration of chloramphenicol.

With chronic concomitant use of paracetamol and zidovudine (AZT), neutropenia often occurs and is probably due to the reduced metabolism of zidovudine. This medicine should therefore only be used at the same time as AZT on medical advice.

Salicylamide may prolong the elimination $t_{1/2}$ of paracetamol.

Isoniazid reduces the paracetamol clearance, with possible potentiation of its action and/or toxicity, by inhibition of its metabolism in the liver.

Paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effect, due to a possible induction of its metabolism in the liver.

Ingestion of probenecid inhibits the binding of paracetamol to glucuronic acid, resulting in a reduction in paracetamol clearance by approximately a factor of 2. The paracetamol dose should be reduced if probenecid is taken concomitantly.

Caution should be exercised with concomitant use of paracetamol and flucloxacillin as concomitant use is associated with high anion gap metabolic acidosis due to pyroglutamic acidosis, especially in patients with risk factors (see section 4.4).

Interference with laboratory tests
Paracetamol may affect phosphotungstate uric acid tests and blood sugar tests by glucose-oxydase-peroxydase.

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 the neuro-development of 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 shortest possible time and at the lowest possible frequency.

Breastfeeding
Paracetamol is excreted in breast milk, but not in clinically significant amount. No negative effects on infants have been reported. Paracetamol may be used by breastfeeding women as long as the recommended dosage is not exceeded. In case of long term use caution should be exercised.

Fertility
No detrimental effects on fertility upon normal use of paracetamol are known.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

At therapeutic doses few undesirable effects occur.

The frequency of undesirable effects is classified 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), not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Rare	Agranulocytosis (long-term use), thrombocytopenia, thrombocytopenic purpura, leucopenia, haemolytic anaemia, platelet disorders, stem cell disorders.
	Very rare	Pancytopenia
Immune system disorders	Rare	Hypersensitivity (excluding angioedema).
	Very rare	Hypersensitivity (angioedema,ventilation difficult, hyperhidrosis, nausea, hypotension, shock, anaphylactic reaction), requiring discontinuation of treatment.
Metabolism and nutrition disorders	Very rare	Hypoglycaemia

	Not known	High anion gap metabolic acidosis
Psychiatric disorders	Rare	Depression NOS, confusion, hallucinations.
Nervous system disorders	Rare	Tremor NOS, headache NOS.
Eye disorders	Rare	Abnormal vision
Cardiac disorders	Rare	Oedema
Respiratory, thoracic and mediastinal disorders	Very rare	Bronchospasm in patients sensitive to aspirin and other NSAIDS
Gastrointestinal disorders	Rare	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
Hepatobiliary disorders	Rare	Hepatic function abnormal, hepatic failure, hepatic necrosis, jaundice.
	Very rare	Hepatotoxicity.
	Administration of 6 grams of paracetamol may already lead to hepatic damage (in children: more than 140 mg/kg); higher doses cause irreversible hepatic necrosis.	
Skin and subcutaneous tissue disorders	Rare	Pruritus, rash, sweating, purpura, angioedema, urticaria.
	Very rare	Serious skin reactions have been reported.
	Not known	Acute generalised exanthemateuspustulosis, toxic necrolysis, drug-induced dermatosis, Stevens-Johnson-syndrome.
Renal and urinary disorders	Very rare	Sterile pyuria (cloudy urine) and renal side effects (severe renal impairment, nephrite interstitial, haematuria, anuresis)
General disorders and administration site conditions	Rare	Dizziness (excluding vertigo), malaise, pyrexia, sedation, drug interaction NOS.
Injury, poisoning and procedural complications	Rare	Overdose and poisoning

NOS= Not otherwise specified

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 products 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

There is a risk of poisoning with paracetamol, especially in the elderly subject's, in young children, in patients with liver disease, in chronic alcoholism, in patients with chronic malnutrition and in patients treated with enzyme inducing drugs. Overdosing may be fatal in these cases.

Liver damage can occur in adults who have 6 g or more of paracetamol especially if the patient has risk factors (see below).

Risk factors:
If the patient
-is on long-term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St. John's wort or other medicines that induce liver enzymes.

Or
-regularly consumes more than the recommended amounts of alcohol.

Or
-is likely to have glutathione deficiency, e.g. due to eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms:
Acute poisoning with paracetamol can proceed in several stages.
In the first two days, the symptoms of paracetamol overdose are nausea, vomiting, anorexia, pallor and abdominal pain. Slight intoxication is limited to these symptoms. When intoxication is more severe, subclinical symptoms as increased liver enzymes appear. Liver damage is clinically manifested after 2-4 days of ingestion. The symptoms, such as painful hepatomegaly, jaundice, encephalopathy coma and coagulation disorders are secondary to hepatic insufficiency. Renal insufficiency (tubular necrosis) is rare. With severe intoxication, metabolic acidosis may occur.

Therapy:
Immediate treatment with local treatment guidelines for paracetamol overdose should be followed.
Immediately after taking an overdose of paracetamol, possibly leading to a serious intoxication, absorption-reducing therapy may be used such as gastric lavage within 1 hour after ingestion or administration of activated charcoal.

N-acetylcysteine (NAC) can be administered as an antidote. For the administration of NAC and further treatment, the concentration of paracetamol in the blood must be determined. Generally, intravenous administration of NAC is preferred and should be continuously administered until paracetamol is no longer detectable. It is important to know that administration of NAC up to 36 hours after the overdose can improve the prognosis.
Oral administration of NAC should not be combined with oral administration activated charcoal.

Liver tests should be performed at the initiation of treatment and every 24 hours to be repeated after the treatment. In most cases, hepatic transaminases will return to normal within two weeks of the overdose with full recovery of the liver function. In rare cases, however, liver transplant may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, Anilides
ATC code: N02BE01.

Paracetamol is an effective antipyretic and analgesic agent. However, it has no anti-inflammatory effect.

The main action of paracetamol is the inhibition of cyclo-oxygenase, an enzyme which is important for the prostaglandin synthesis. Central nervous system cyclo-oxygenase is more sensitive for paracetamol than peripheral cyclo-oxygenase and this explains why paracetamol has an antipyretic and analgesic efficacy without a conspicuous peripheral anti-inflammatory activity.

5.2 Pharmacokinetic properties

Absorption

After oral administration paracetamol is rapidly and almost completely absorbed. Peak plasma concentrations are reached after 30 minutes to 2 hours.

Distribution
Paracetamol is distributed rapidly throughout all tissues. Concentrations are comparable in blood, saliva and plasma.

The volume of distribution of paracetamol is approximately 1 L/kg bodyweight. At therapeutic doses protein binding is negligible.

Biotransformation
In adults paracetamol is conjugated in the liver with glucuronic acid (~60%), sulphate (~35%) conjugates. The latter route is rapidly saturated at doses higher than the therapeutic dose. A minor route, catalyzed by the cytochrome P450, results in the formation of an intermediate reagent (N-acetyl-p-benzoquinoneimine) which under normal conditions of use is rapidly detoxified by glutathione and eliminated in the urine, after conjugation with cysteine (~3%) and mercaptopuric acid.

In neonates and children <12 years sulphate conjugation is the main elimination route and glucuronidation is lower than in adults. Total elimination in children is comparable to that in adults, due to an increased capacity for sulphate conjugation.

Elimination
Elimination of paracetamol is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, predominantly as the glucuronide (60 to 80%) and the sulphate (20 to 30%) conjugates. Less than 5% is eliminated in unchanged form. The elimination half-life is about 2 hours.

In cases of renal or hepatic insufficiency, after overdose, and in neonates the elimination half-life of paracetamol is delayed. The maximum effect is equivalent with plasma concentrations. For elderly patients, the capacity for conjugation is not modified.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Extensive studies revealed no evidence of a relevant genotoxic risk for paracetamol within the therapeutic, i.e. non-toxic, dose range.

Long-term studies on rats and mice do not indicate any relevant tumorigenic effects at non-hepatotoxic doses of paracetamol.

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

Tablet core
Pregelatinized maize starch
Povidone K-30
Sodium maize starch glycolate (Type-A)
Stearic acid (E570)

Film-coating
Hypromellose (E464)
Macrogol 400 (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister packs: 30 months.
HDPE bottle packs: 36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear, transparent PVC/ Aluminium blister pack in an outer carton box containing 10 or 12 tablets per blister.

Pack sizes: 10 film-coated tablets (one blister in one carton)
12 film-coated tablets (one blister in one carton)

Clear, transparent PVdC coated PVC/Aluminium blister pack in an outer carton box containing 10 or 12 tablets per blister.

Pack sizes: 20 film-coated tablets (two blisters in one carton)
24 film-coated tablets (two blisters in one carton)

White opaque HDPE bottle packs with white polypropylene closure.

Pack sizes: 24 film-coated tablets
100 film-coated tablets
300 film-coated tablets
500 film-coated tablets
1000 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
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8 MARKETING AUTHORISATION NUMBER

PA0126/020/008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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March 2026