Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paralief Max 1000 mg Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains 1000mg of paracetamol.

Excipients with known effects:

Each effervescent tablet contains 533.51mg of sodium

Each effervescent tablet contains 10mg of aspartame.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Effervescent tablet

White to off white coloured circular flat-faced, bevelled tablets plain on both sides. Diameter: 25.2mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term symptomatic treatment of mild to moderate pain and/or fever in adults and adolescents aged 16 years and above.

4.2 Posology and method of administration

Posology

Paediatric population

- Dose depends on body weight and age. A single dose ranges from 10 to 15 mg/kg bodyweight. The maximum total daily dose is 60 mg/kg body weight.
- Children and adolescents below 16 years of age: this product is not recommended in patients aged less than 16 years.
- Adolescents of 16 to 18 years and weighing more than 50 kg: as adults.

Adults
For adults and adolescents weighing more than 50 kg (aged 16 years and older) the usual single dose is 1 tablet at a time, to be repeated every 6 hours as needed, the maximum being 4 tablets per day (paracetamol 4000 mg per 24 hours).

Paracetamol 1000mg tablets are not suitable for patients weighing less than 50 kg. More appropriate forms (i.e. 500 mg tablets) are available on the market for use.

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

Paracetamol 1000 mg tablets are not suitable for patients with renal insufficiency when reduced dose is required. More appropriate forms (i.e. 500 mg tablets) are available in the market for use.

Hepatic impairment
In patients with hepatic impairment or Gilbert´s Syndrome, the dose should be reduced or the dosing interval prolonged. Paracetamol 1000 mg tablets are not suitable for patients with hepatic insufficiency when reduced dose is required. More appropriate forms (i.e. 500 mg tablets) are available in the market for use. 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:

• Chronic alcoholism
• Dehydration
• Chronic malnutrition

Method of administration
Oral use. Place the tablets in a full tumbler of water and allow to dissolve completely before swallowing.

After dissolving the tablets, a slightly opalescent solution will be produced.

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

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 unconsciousness does not occur. However, medical assistance should be sought immediately. Prolonged use except under medical supervision may be harmful. In children treated with 60mg/kg daily of paracetamol, the combination with another antipyretic is not justified except in the case of ineffectiveness.

Renal and hepatic impairment
Caution is advised in the administration of paracetamol to patients with moderate and severe renal insufficiency, mild to moderate hepatocellular insufficiency (including Gilbert's syndrome), severe hepatic insufficiency (***Child-Pugh >9***), acute hepatitis, concomitant treatment with medicinal products affecting hepatic functions, glucose-6-phosphatedehydrogenase deficiency, haemolytic anaemia, dehydration, alcohol abuse and chronic malnutrition (see section 4.2).

Alcohol usage
The hazards of overdose are greater in those with non-cirrhotic alcoholic liver disease. Caution should be exercised in cases of chronic alcoholism. The daily dose should not exceed 2000 mg in such case. Alcohol should not be used during the treatment with paracetamol.

"Caution is advised in asthmatic patients sensitive to aspirin (acetylsalicylic acid), because light reaction bronchospasm with paracetamol (cross reaction) has been reported in less than 5% of the patients tested"

Other medications and withdrawal
Abrupt discontinuation of long-term use of high-dosed analgesics, taken not as directed, may cause headache, tiredness, muscular pain, nervousness and vegetative symptoms. The withdrawal symptoms subside within a few days. Patients should be advised to consult their doctor if headaches become persistent.

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, sepsis 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 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.

This medicinal product contains 533.51 mg sodium per effervescent tablet, equivalent to 26.68% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This product also contains aspartame, a source of phenylalanine. May be harmful to people with phenylketonuria.

Do not exceed the stated dose.

If symptoms persist consult a doctor.

Treatment with an antidote is advised if an overdose is suspected.

Immediate medical advice should be sought in the event of overdosage even if the patient feels well because of the risk delayed serious liver damage.

This product should not be used for more than 10 consecutive days without a prescription. Liver and kidney damage cannot be excluded with prolonged use or excessive doses (more than 2 gram per day).

Paediatric population
Paracetamol effervescent tablets should not be administered in children and adolescents below 16 years of age and under 50 kg body weight.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
The anticoagulant effect of warfarin and other coumarins may be enhanced by regular use of paracetamol with increased risk of bleeding. The effect may occur already at daily doses of 2000 mg after 3 days. Occasional doses have no significant effect on bleeding tendency. Increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.

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).

Pharmacokinetic interactions
Use of substances that induce liver enzymes, such as carbamazepine, phenytoin, phenobarbital, rifampicin and St John's wort (Hypericum perforatum) can increase the hepatotoxicity of paracetamol due to increased and more rapid formation of toxic metabolites. Therefore, caution should be taken in case of concomitant use of enzyme inducing substances.

Probenecid nearly halves the clearance of paracetamol by inhibiting its conjugation with glucuronic acid. This probably means that the dose of paracetamol can be halved when being given at the same time as probenecid.

Concurrent intake of medicinal products that accelerate gastric emptying, such as metoclopramide or domperidone, accelerates the absorption and onset of effect of paracetamol.

The absorption of paracetamol is reduced by cholestyramine. Cholestyramine should not be given within one hour if maximum analgesic effect is to be obtained.

Isoniazid affects the pharmacokinetics of paracetamol with possible potentiation of liver toxicity.

Paracetamol may affect the pharmacokinetics of chloramphenicol. Therefore an analysis of chloramphenicol in plasma is recommended in the event of combination treatment with chloramphenicol for injection.

Interference with laboratory tests
Paracetamol may affect uric acid tests by wolframato phosphoric acid, and blood sugar tests by glucose-oxidase-peroxidase.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women indicate neither malformative, nor foeto/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
After oral administration, paracetamol is excreted into breast milk in small quantities. No undesirable effects on nursing infants have been reported. Consequently, paracetamol may be used in breast-feeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency using the following convention should be: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency	**System**	**Symptoms**
Rare >1/10000 - < 1/1000	Blood and lymphatic system disorders	Platelet disorders, stem cell disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia, pancytopenia, methaemoglobenaemia
	Immune system disorders	Allergies (excluding angioedema).
	Psychiatric disorders	Depression NOS, confusion, hallucinations.
	Nervous system disorders	Tremor NOS, headache NOS.
	Eye disorders	Abnormal vision.
	Cardiac disorders	Oedema.
	Gastrointestinal disorders	Haemorrhage NOS, abdominal pain NOS, diarrhoea NOS, nausea, vomiting.
	Hepato-biliary disorders	Abnormal Hepatic function, hepatic failure, hepatic necrosis, jaundice.
	Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria
	General disorders and administration site conditions	Dizziness (excluding vertigo), malaise,

		pyrexia, sedation, drug interaction NOS.
	Injury, poisoning and procedural complications	Overdose and poisoning
Very Rare (< 10,000)	Respiratory, thoracic and mediastinal disorders	Bronchospasm
	Hepato-biliary disorders	hepatotoxicity
	General disorders and administration site conditions	hypersensitivity reaction (requiring discontinuation of treatment)
	Metabolism and nutrition disorders	Hypoglycemia
	Renal and urinary disorders	Sterile pyuria (cloudy urine) and renal side effects
	Skin and subcutaneous disorders	Very rare cases of serious skin reactions
Not known (cannot be estimated from the available data)	Metabolism and nutrition disorders	High anion gap metabolic acidosis

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.

Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis, Stevens Johnson syndrome, erythema multiforme, oedema of the larynx, anaphylactic shock, anaemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastro intestinal effects and vertigo have been reported.

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

There is a risk of poisoning, particularly in elderly subjects, in young adolescents, in patients with liver disease, in cases of chronic alcoholism, in patients with chronic malnutrition. Overdosing may be fatal.

Liver damage is possible in adults who have taken 10g or more of paracetamol. Ingestion of 5g or more of paracetamol may lead to liver damage 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 drugs that induce liver enzymes.
- Or Regularly consumes ethanol in excess of recommended amounts.
- Or Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

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.

Management

Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable). Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however, the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time. If required the patient should be given intravenous N-acetylcysteine, in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

High doses of sodium bicarbonate may be expected to induce gastrointestinal symptoms including belching and nausea. In addition, high doses of sodium bicarbonate may cause hypernatraemia; electrolytes should be monitored and patients managed accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesics and antipyretics; anilides

ATC code: N02BE01

5.2 Pharmacokinetic properties

Absorption
The absorption of paracetamol by the oral route is rapid and complete. Maximum plasma concentrations are reached 30 to 60 minutes following ingestion.

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

Biotransformation
Paracetamol is metabolized mainly in the liver following two major metabolic pathways: glucuronic acid and sulfuric acid 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 and mercaptopuric acid. Conversely, when massive intoxication occurs, the quantity of this toxic metabolite is increased.

Elimination
Elimination is essentially through the urine. 90% of the ingested dose is eliminated via the kidneys within 24 hours, principally as glucuronide (60 to 80%) and sulphate conjugates (20 to 30%). Less than 5% is eliminated in unchanged form.

Elimination half life is about 2 hours.

Special patient groups
Renal impairment
In cases of severe renal insufficiency (creatinine clearance lower than 10 ml/min) the elimination of paracetamol and its metabolites is delayed.

Elderly

The capacity for conjugation is not modified.

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

Citric acid (anhydrous) (E330)
Povidone
Sodium bicarbonate (E500)
Sodium saccharin (E954)
Sodium carbonate (anhydrous) (E500)
Simeticone (E900)
Polysorbate 80 (E443)
Aspartame (E951)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

The solution is stable up to 8 hours below 25^{o}C after dissolving the tablet.

6.4 Special precautions for storage

This medicinal product does not require any special temperature conditions.

Store in the original package to protect from light and moisture.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

4-ply laminate - PPFP (glassine paper/polythene/aluminium foil/polythene) or 4-ply laminate- Surlyn (glassine paper/polythene/ aluminium foil/ Surlyn) strips packed into cardboard cartons.

Pack size(s) for strip pack: - 8, 10, 12, 16, 20, 32, 40, 50, 60, 100 units.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After dissolving the tablets, a slightly opalescent solution will be produced.
There are no special requirements for handling of product.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
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8 MARKETING AUTHORISATION NUMBER

PA0126/020/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2015
Date of last renewal: 26th June 2020

10 DATE OF REVISION OF THE TEXT

March 2025