Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paralief Hot Lemon Drink 600 mg powder for oral solution in sachet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 600 mg paracetamol.

Excipients with known effect
Each sachet contains 3.8 g sucrose and 95 mg aspartame (E951).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for oral solution in sachet

White to slightly yellow powder with the smell of lemon.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For relief of symptoms of influenza and feverish colds (incl. headache, aches and pains), menstrual pain and toothache.

For children aged 12 years or older, adolescents and adults.

4.2 Posology and method of administration

Posology
Single dose: 1 sachet (600 mg paracetamol); maximum of 4 doses in 24 hours with at least 6 hours between doses.

A single dose of 1 sachet may not be exceeded.

If other paracetamol-containing medicines are taken concomitantly, the maximum recommended daily dose of paracetamol must not be exceeded.

Dosing after meals may lead to a delayed onset of action.

Special populations

Elderly people
No specific dose adjustment is required.

Hepatic impairment and mild renal impairment
Dose must be reduced by prolongation of dosing interval in patients with impaired hepatic or renal function and Gilbert's syndrome.

Severe renal impairment
In cases of severe renal impairment (creatinine clearance < 10 ml/min), an interval of at least 8 hours must be respected between doses.

Patients weighing less than 40 kg

Paralief Hot Lemon Drink may not be used in patients weighing less than 40 kg, as the dosage strength is not suitable for these patient groups. More appropriate dosage strengths and/or pharmaceutical forms of paracetamol are available for such patient groups.

Paediatric population
Not for use in children under 12 years. More appropriate dosage strengths and/or pharmaceutical forms of paracetamol are available for such patient groups.

Method of administration
First, bring water to boil and let cool for about 10 minutes.
Empty the content of one sachet into a cup, top with the hot water and stir well. A slightly cloudy, colourless to light yellowish solution will be obtained.
Drink after sufficient cooling down to a drinkable temperature.

Duration of treatment
Paralief Hot Lemon Drink should not be taken for more than 3 days without the advice of a doctor or dentist. A doctor should be consulted if symptoms persist beyond 3 days.

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

Care is advised in the administration of paracetamol to patients with severe renal or severe hepatic impairment. The hazard of overdose is greater in those with non-cirrhotic alcoholic liver disease. Patients should be advised not to take other paracetamol-containing products concurrently to avoid the risk of overdosing.

Paracetamol should be used with particular caution in the following cases:

• hepatocellular insufficiency (including Gilbert's syndrome)
• chronic alcohol abuse
• severe renal insufficiency (creatinine clearance < 10 ml/min, see section 4.2)
• concomitant treatment with medicinal products affecting hepatic function
• glucose-6-phosphate dehydrogenase deficiency
• haemolytic anaemia
• glutathione deficiency
• dehydration
• chronic malnutrition

A doctor must be consulted in the event of high fever, signs of secondary infection or persistence of symptoms beyond 3 days.

Without the advice of a doctor or dentist, medications containing paracetamol should generally only be used for a few days and at lower doses.

Prolonged use of any type of painkiller for headaches can make them worse. If this situation is experienced or suspected, medical advice should be obtained and treatment should be discontinued. The diagnosis of medication overuse headache (MOH) should be suspected in patients who have frequent or daily headaches despite (or because of) the regular use of headache medications.

In general, habitual analgesic use may lead to permanent renal damage with the risk of renal failure (analgesic nephropathy), particularly if several analgesic substances are combined.

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.

Excipients
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

1 sachet contains 3.8 g sucrose. This should be taken into consideration in patients with diabetes mellitus.

Contains aspartame as a source of phenylalanine and may be harmful in patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interactions

□∀ Probenecid intake inhibits the binding of paracetamol to glucuronic acid, and thereby leads to a reduction in paracetamol clearance by approximately a factor of 2. The paracetamol dose should be reduced in cases of concomitant probenecid intake.
• Particular caution is advised in patients taking concomitant medications that cause enzyme induction, or potentially hepatotoxic substances (see section 4.9).
• With concomitant use of paracetamol and AZT (zidovudine), there is increased susceptibility for the development of neutropenia. This medicinal product may therefore only be used together with AZT on the advice of a doctor.
• Concomitant intake of medications that accelerate gastric emptying, e.g. metoclopramide, causes an acceleration in the absorption and onset of action of paracetamol.
• If agents that decelerate gastric emptying, e.g. propantheline, are concomitantly taken, the absorption and onset of action of paracetamol may be delayed.
• Colestyramine reduces paracetamol absorption.
• The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding.
• 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).

Effects on laboratory values
Paracetamol intake can affect uric acid assays that use phosphotungstic acid, and determination of blood glucose via 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
Following oral administration, small amounts of paracetamol are excreted into breast milk. During breast-feeding, there are no undesirable effects or side effects known to date. Paracetamol may be administered at therapeutic doses during breast-feeding.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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), not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

Blood and lymphatic system disorders
Very rare: Changes in the blood picture (e.g. thrombocytopenia, agranulocytosis).

Immune system disorders
Very rare: Bronchospasm (analgesic-induced asthma) *, hypersensitivity reactions **.

Hepatobiliary disorders
Rare: Increase in liver transaminases

Skin and subcutaneous tissue disorders
Very rare cases of serious skin reactions have been reported.

* In predisposed individuals.
** Ranging from simple skin erythema right up to urticaria and anaphylactic shock.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

Symptoms of intoxication
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, cachexi

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, anilides
ATC code: N02BE01

Mechanism of action
The analgesic and antipyretic mechanism of action of paracetamol has not been clearly elucidated. A central and peripheral action is probable. Marked inhibition of cerebral prostaglandin synthesis has been demonstrated, whereas peripheral prostaglandin synthesis is only weakly inhibited. Furthermore, paracetamol inhibits the effect of endogenous pyrogens on the hypothalamic temperature regulation centre.

5.2 Pharmacokinetic properties

Absorption
After oral administration, paracetamol is rapidly and completely absorbed. Peak plasma concentrations are reached within 30-60 minutes after ingestion. Paracetamol absorption is 68-88 % following rectal administration; peak plasma concentrations are reached after 3-4 hours.

Distribution
Paracetamol is rapidly distributed to all tissues. Blood, plasma and saliva concentrations are comparable. Plasma protein binding is low.

Biotransformation
Paracetamol is predominantly metabolised in the liver, mainly via two pathways: conjugation with glucuronic acid and sulphuric acid. At doses exceeding the therapeutic dose, the latter pathway is rapidly saturated. To a minor extent, metabolism also occurs via the catalyst cytochrome P 450 (mainly CYP2E1), resulting in the formation of the N-acetyl-p-benzoquinone imine metabolite, which in general is rapidly detoxified by glutathione and bound by cysteine and mercapturic acid. In cases of massive intoxication, the amount of this toxic metabolite is increased.

Elimination
Paracetamol is predominantly excreted in the urine. 90 % of the absorbed amount is excreted via the kidneys within 24 hours, mainly as glucuronides (60-80 %) and sulphate conjugates (20-30 %). Less than 5 % is excreted in unchanged form. The elimination half-life is approximately 2 hours. The half-life is prolonged in cases of hepatic and renal dysfunction, following overdosage and in neonates. The peak effect and mean duration of action (4-6 hours) roughly correlate with plasma concentrations.

Renal impairment
In cases of severe renal impairment (creatinine clearance < 10 ml/min), excretion of paracetamol and its metabolites is delayed.

Older people
The capacity for conjugation is unchanged.

5.3 Preclinical safety data

In animal trials, performed on rats and mice to investigate the acute, subchronic and chronic toxicity of paracetamol, the following were observed: gastrointestinal lesions, changes in the blood count, degenerative changes in the hepatic/renal parenchyma and necrosis. These changes can be explained by the mechanism of action on the one hand, and by paracetamol

metabolism on the other. Those metabolites presumed to be the cause of toxic effects and subsequent organic changes, have also been found in humans. In addition, during long-term use (i.e. one year) within the maximum therapeutic dose range, very rare cases of reversible chronic aggressive hepatitis were observed. At subtoxic doses, symptoms of intoxication can occur after three weeks of use. Paracetamol should therefore not be taken at higher doses or over prolonged periods.

Extensive studies revealed no evidence of any 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 with non-hepatotoxic doses of paracetamol. Based on animal studies and human experience to date, there is no evidence of any teratogenicity. Paracetamol crosses the placenta.

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

Ascorbic acid
Aspartame (E951)
Anhydrous citric acid
Ethylcellulose
Colloidal anhydrous silica
Sucrose
Lemon flavouring (consisting of citral, citronella oil, coriander seed oil, gum arabic and lime oil distilled)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Sachet consisting of aluminium foil, coated with paper on the outer side and with LDPE-foil on the inner side

Pack size: 5 and 10 sachets

6.6 Special precautions for disposal

Bring water to boil and let cool for about 10 minutes.
Empty the content of one sachet into a cup, top with the hot water and stir well. A slightly cloudy, colourless to light yellowish solution will be obtained. Allow to cool before drinking.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th September 2017
Date of last renewal: 15th August 2022

10 DATE OF REVISION OF THE TEXT

May 2022