Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Paralief Sinus Tablets Paracetamol 500 mg Pseudoephedrine hydrochloride 30 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of paracetamol and 30 mg of pseudoephedrine hydrochloride

Excipient(s) with known effect
Each tablet contains no more than 0,882 mg of sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Approximately 18 mm plain, white to off-white, capsule shaped tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paralief Sinus Tablets are indicated for the short term symptomatic treatment of nasal and sinus congestion associated with the symptoms of cold and flu, such as mild pain, headache and/or fever. Paralief Sinus Tablets are indicated in adults and adolescents aged 15 years and over.

4.2 Posology and method of administration

Adults and adolescents aged 15 years and over:
Oral. One to two tablets, every four to six hours, two to three times a day. Maximum daily dose: 6 tablets (i.e. 180 mg pseudoephedrine hydrochloride, 3 g paracetamol).

Children and adolescents aged under 15 years:
Paralief Sinus Tablets are not recommended in children and adolescents aged under 15 years.

The Elderly:
Experience has indicated that normal adult dosage is appropriate. However in frail, immobile, elderly patients, a reduction in the amount or frequency of dosing may be appropriate.

Hepatic dysfunction
In patients with impaired hepatic function or Gilbert's Syndrome, the dose must be reduced or the dosing interval prolonged.

Renal dysfunction:
Caution should be exercised when administering Paralief Sinus Tablets to patients with moderate to severe renal impairment, particularly if accompanied by cardiovascular disease. It is recommended, when giving paracetamol to patients with renal failure, to reduce the dose and to increase the minimum interval between each administration to at least 6 hours.

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

Patients should seek medical advice if symptoms persist for more than 3 days or worsen.

The maximum daily dose of paracetamol should not exceed 2g in the following situations unless directed by a physician:

- Weight less than 50kg
- Hepatic impairment
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

4.3 Contraindications

- Hypersensitivity to the actives substances or to any of the excipients listed in section 6.1.
- Coronary artery disease, hypertension and cardiovascular disease.
- Patients taking other sympathomimetic drugs such as decongestants, appetite suppressants and amphetamine-like psychostimulants (see section 4.5).
- Patients who are taking or have taken monoamine oxidase inhibitors (MAOIs) within the last two weeks. Patients taking tricyclic antidepressants (see section 4.5). The concomitant use of pseudoephedrine and this type of product may occasionally cause a rise in blood pressure.
- Hyperthyroidism.
- Closed angle glaucoma.
- Urinary retention.
- Pheochromocytoma.
- Patients taking beta-blocking drugs (see section 4.5).
- The product should not be used concurrently with furazolidone.

4.4 Special warnings and precautions for use

Caution should be exercised in the administration of paracetamol to patients with moderate and severe renal insufficiency (particularly if accompanied by cardiovascular disease)., 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-phosphate dehydrogenase deficiency, haemolytic anaemia, dehydration, alcohol abuse, chronic malnutrition and weight <50kg.
Contains paracetamol. Patients should not take any other paracetamol-containing products concurrently due to the risk of severe liver damage in case of overdose.
Following long-term, high-dose, incorrect use of analgesics, headaches may occur which should not be treated using higher doses of analgesics.
In general, habitual intake of analgesics, particularly a combination of several analgesic substances, can lead to permanent renal damage with the risk of renal failure.
Abrupt discontinuation following long-term, high-dose, incorrect use of analgesics may lead to headaches, fatigue, muscle pain, nervousness and autonomic symptoms. These withdrawal symptoms resolve within a few days. Until this time, further intake of analgesics should be avoided and not restarted without medical advice.
Patients should not take other sympathomimetic containing products concomitantly, including other nasal or eye decongestant products.
Alcoholic beverages should be avoided while taking this medicine. Paracetamol should be given with caution to patients with alcohol dependence (see section 4.5). The hazards of overdose are greater in those non-cirrhotic alcoholic liver disease.
As with other sympathomimetic agents this medicine should be used with caution in patients with:

- Diabetes,

- Prostatic hypertrophy, as they may be susceptible to urinary retention and dysuria,
- Occlusive vascular disease (e.g. Raynaud's Phenomenon),
- Psychosis,
- Chronic cough, asthma, or emphysema.

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.

Severe skin reactions

Severe skin reactions such as acute generalized exanthematous pustulosis (AGEP) may occur with pseudoephedrine-containing products. This acute pustular eruption may occur within the first 2 days of treatment, with fever, and numerous, small, mostly non-follicular pustules arising on a widespread oedematous erythema and mainly localized on the skin folds, trunk, and upper extremities. Patients should be carefully monitored. If signs and symptoms such as pyrexia, erythema, or many small pustules are observed, administration of Paralief Sinus Tablets should be discontinued and appropriate measures taken if needed.
Elderly patients may be particularly sensitive to central nervous system effects of pseudoephedrine.
This medicine is recommended when the symptoms (pain and/or fever, congestion) are present. It should be used only for a few days. Patients should seek medical advice if symptoms persist for more than 3 days or worsen.
In case of surgery, it is advisable to stop treatment a few days before. Risk of hypertensive crisis is increased if halogenated anaesthetics are used (see section 4.5).

Ischaemic colitis
Some cases of ischaemic colitis have been reported with pseudoephedrine. Pseudoephedrine should be discontinued and medical advice sought if sudden abdominal pain, rectal bleeding or other symptoms of ischaemic colitis develop.

Ischaemic optic neuropathy
Cases of ischaemic optic neuropathy have been reported with pseudoephedrine. Pseudoephedrine should be discontinued if sudden loss of vision or decreased visual acuity such as scotoma occurs.

Paralief Sinus contains sodium
This medicine contains less than 1 mmol sodium (23mg) per Tablet, that is to say essentially 'sodium-free'.

Paediatric population
This product should not be given children or adolescents aged under 15 years.

Warning concerning doping misuse
Pseudoephedrine may induce positive results in certain anti-doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

Paracetamol
The anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol, with increased risk of bleeding. Occasional use of paracetamol has no significant effect.
Metoclopramide or domperidone may increase the rate of absorption of paracetamol.
The tuberculosis treatments rifampicin and isoniazid may increase the hepatotoxicity of paracetamol.
The half-life of chloramphenicol may be prolonged by paracetamol. However, topical chloramphenicol may be used concomitantly when used to treat eye infections.
Antiepileptics such as phenytoin, phenobarbital and carbamazepine (enzyme-inducing medicines) may increase the risk of liver damage.

Chronic ingestion of anticonvulsants or oral steroid contraceptives induce liver enzymes and may prevent attainment of therapeutic paracetamol levels by increasing first pass metabolism or clearance.
Paracetamol may decrease the bioavailability of lamotrigine, with possible reduction of its effect, due to a possible induction of its metabolism in the liver.
Cholestyramine may reduce the absorption of paracetamol. Cholestyramine should not be given within one hour following paracetamol intake.
Regular use of paracetamol simultaneously with zidovudine may cause neutropenia and increases the risk of liver damage.
The gout treatment probenecid reduces the clearance of paracetamol, so the dose of paracetamol may be reduced in case of concomitant treatment.

Patients who have taken barbiturates, tricyclic antidepressants and alcohol may show diminished ability to metabolise large doses of paracetamol, the plasma half-life of which can be prolonged. Alcohol can increase the hepatotoxicity of paracetamol overdose and may have contributed to the acute pancreatitis reported in one patient who had taken an overdose of paracetamol (see section 4.4).
Paracetamol may affect phosphotungstate uric acid tests and blood sugar tests.
Salicylates/acetylsalicylic acid may prolong the elimination t1/2 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).
Pharmacological interactions involving paracetamol with a number of other drugs have been reported. These are considered to be of unlikely clinical significance in acute use at the dosage regimen.

Pseudoephedrine
Concomitant use of Pseudoephedrine with tricyclic antidepressants, sympathomimetic agents (such as decongestants, appetite suppressants and amphetamine-like psychostimulants) or with monoamine oxidase inhibitors, which interferes with the catabolism of sympathomimetic amines, may occasionally cause a rise in blood pressure, [See section 4.3]. Use is contraindicated in patients who are taking or have taken MAOIs within the past two weeks (see section 4.3).
Concomitant use of pseudoephedrine with other sympathomimetic agents can increase the risk of cardiovascular side effects.
Pseudoephedrine may reduce the efficacy of alpha and beta blocking drugs (see section 4.3) and other antihypertensive drugs (e.g. bretylium, betanidine, debrisoquine, guanethidine, reserpine, methyldopa) [See section 4.4]. The risk of hypertension and other cardiovascular side effects may be increased.
Pseudoephedrine may interact with halogenated anaesthetics such as cyclopropane, halothane, enflurane, isoflurane (see section 4.4).
Concomitant use of pseudoephedrine with digoxin and cardiac glycosides may increase the risk of irregular heartbeat or heart attack.
Ergot alkaloids (ergotamine and methylsergide): there may be an increased risk of ergotism.
Concomitant use with linezolid may increase the risk of hypertension.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well controlled clinical studies in pregnant or breast feeding women for the combination of paracetamol and pseudoephedrine.
As a precautionary measure, it is preferable to avoid the use of paracetamol pseudoephedrine during pregnancy.

Pseudoephedrine
There are limited data on the use of pseudoephedrine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). The use of pseudoephedrine decreases maternal uterine blood flow and therefore as a precautionary measure, it is preferable to avoid the use of pseudoephedrine in pregnancy.

Paracetamol
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
This medicine should be avoided during lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the nursing infant.

Pseudoephedrine
Pseudoephedrine is excreted in breast milk in small amounts but the effect of this on breast-fed infants is not known. It has been estimated that 0.5 to 0.7% of a single 60 mg dose of pseudoephedrine ingested by a mother will be excreted in the breast milk over 24 hours.

Paracetamol
Paracetamol is excreted in breast milk but not in a clinically significant amount. A pharmacokinetic study of paracetamol in 12 nursing mothers revealed that less than 1% of a 650 mg oral dose of paracetamol appeared in the breast milk. Similar findings have been reported in other studies. Therefore, maternal ingestion of a therapeutic dose of paracetamol does not appear to present a risk to the neonate/infant.

Fertility
Pseudoephedrine
No studies have been conducted in animals to determine whether pseudoephedrine has the potential to impair fertility.

There is no information of the effect of Paralief Sinus Tablets on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. If affected by dizziness, patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

Paracetamol
Adverse events from historical clinical trial data are both infrequent and from limited patient exposure. Events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by MedDRA System Organ Class. Due to limited clinical trial data, the frequency of these adverse events is unknown (cannot be estimated from available data), but post-marketing experience indicates that adverse reactions to paracetamol are rare (≥1/10,000 to <1/1,000) and serious reactions are very rare (<1/10,000).

Paracetamol has been widely used and, when taken at the usual recommended dosage, side effects are mild and infrequent and reports of adverse reactions are rare.

Chronic hepatic necrosis has been reported in a patient who took daily therapeutic dosages of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. A review of a group of patients with chronic active hepatitis failed to reveal differences in the abnormalities of liver function in those who were long-term users of paracetamol nor was the control of their disease improved after paracetamol withdrawal.

Nephrotoxic effects following therapeutic dosages of paracetamol are uncommon. Papillary necrosis has been reported after prolonged administration.

Pseudoephedrine
Serious side effects associated with the use of pseudoephedrine are rare.

Urinary retention has occasionally been reported in men receiving pseudoephedrine; prostatic enlargement could have been an important predisposing factor.

Pseudoephedrine – System of organ classifications	
Nervous system disorders:	Central nervous system stimulation sleep disturbance, hallucinations
Skin and subcutaneous tissue disorder :	Skin rashes (with or without itching) - pruritus, erythema, urticaria, allergic dermatitis Severe skin reactions, including acute generalized exanthematous pustulosis (AGEP) ,with unknown frequency.
Renal and urinary disorders:	Urinary retention particularly in patients with prostatic hypertrophy.
Cardiac disorders	Cardiac effects (e.g. tachycardia)
Vascular disorders	Increase in blood pressure, although not in controlled hypertension
Gastrointestinal disorders	Ischaemic colitis (frequency unknown)
Eye disorders	Ischaemic optic neuropathy (frequency unknown)
Paracetamol – System of organ classifications	
Blood and the lymphatic system disorders:	Thrombocytopenic purpura, haemolytic anaemia, agranulocytosis, Thrombocytopenia, agranulocytosis, pancytopenia, leucopenia, neutropenia. These are not necessarily causally related to paracetamol
Hepato-biliary disorders:	Chronic hepatic necrosis, liver damage Nephrotoxic effects Papillary necrosis
Skin and subcutaneous:	Skin rashes (with or without itching) Very rare cases of serious skin reactions have been reported.
Social circumstances	Over dosage
Immune system disorders	Hypersensitivity, including anaphylactic reactions, angioedema, Steven Johnson syndrome and bronchospasm*.
Gastrointestinal disorders	Abdominal discomfort, diarrhoea, nausea and vomiting

*There have been cases of bronchospasm with paracetamol, but these are more likely in asthmatics sensitive to aspirin or other NSAIDs.

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

Pseudoephedrine
As with other sympathomimetic agents, symptoms and signs of pseudoephedrine overdose include irritability, restlessness, tremor, convulsions, palpitations, hypertension and difficulty with micturition.

Measures should be taken to maintain and support respiration and control convulsions. Gastric lavage should be performed if indicated. Catheterisation of the bladder may be necessary. If desired, the elimination of pseudoephedrine can be accelerated by acid diuresis or by dialysis.
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.

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

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 in a single administration in adults or in children 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 adults who have taken more than the recommended amounts of paracetamol. It is considered that excess quantities of toxic metabolite (usually adequately detoxified by glutathione when normal doses of paracetamol are ingested), become irreversibly bound to liver tissue.

Some patients may be at increased risk of liver damage from paracetamol toxicity.

Risk Factors include:
If the patient
A. Is on long term treatment with carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.

Or

B. Regularly consumes ethanol in excess of recommended amounts.

Or

C. Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

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>150mg/kg paracetamol has been taken within 1 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Paracetamol, combinations excluding psycholeptics: N02BE51
Other cold preparations: R05X

Pseudoephedrine
Pseudoephedrine has direct and indirect sympathomimetic activity and is an effective upper respiratory tract decongestant. Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation of systolic blood pressure and considerably less potent in causing stimulation of the central nervous system.

Paracetamol
Paracetamol has analgesic and antipyretic actions but only weak anti-inflammatory properties. This may be explained by presence of cellular peroxides at sites of inflammation which prevent inhibition of cyclo-oxygenase by paracetamol at other sites associated with low levels of cellular peroxides, e.g. pain, fever, paracetamol can successfully inhibit prostaglandin biosynthesis.

5.2 Pharmacokinetic properties

Pseudoephedrine
Absorption
Pseudoephedrine is rapidly and completely absorbed from the gastrointestinal tract after oral administration with no presystemic metabolism. Peak plasma levels are achieved after 1-2 hours.

Biotransformation
Pseudoephedrine is partly metabolised in the liver by N-demethylation to norpseudoephedrine, an active metabolite.

Elimination
Pseudoephedrine and its metabolite are excreted in the urine: 55% to 75% of a dose is excreted unchanged. The rate of urinary excretion of pseudoephedrine is accelerated when the urine is acidified. Conversely as the urine pH increases, the rate of urinary excretion is slowed.

Paracetamol
Absorption
Peak plasma paracetamol concentration usually occurs between 30 and 90 minutes after oral ingestion.

Distribution
Paracetamol is distributed uniformly throughout most body fluids and is only 15 to 25 per cent bound to plasma proteins. The plasma half-life of paracetamol after therapeutic doses is in the range of 1 to 3 hours.

Renal insufficiency
In cases of renal failure (GFR≤50ml/min), the elimination of paracetamol is slightly delayed, the elimination half-life ranging from 2 to 5.3 hours. For the glucuronide and sulphate conjugates, the elimination rate is 3 times slower in subjects with severe renal impairment than in healthy subjects. Therefore, it is recommended, when giving paracetamol to patients with renal failure (GFR≤50ml/min), to reduce the dose and to increase the minimum interval between each administration to at least 6 hours.

5.3 Preclinical safety data

Mutagenicity
Paracetamol
In vivo mutagenicity tests of paracetamol in mammals are limited and show conflicting results. Therefore, there is insufficient information to determine whether paracetamol poses a mutagenic risk to man.

Paracetamol has been found to be non-mutagenic in bacterial mutagenicity assays, although a clear clastogenic effect has been observed in mammalian cells *in vitro* following exposure to paracetamol (3 and 10 mM for 2 hr).

Pseudoephedrine
The results of a wide range of tests indicate that pseudoephedrine does not pose a mutagenic risk to man.

Carcinogenicity
Paracetamol
There is inadequate evidence to determine the carcinogenic potential of paracetamol in humans. A positive association between the use of paracetamol and cancer of the ureter (but not of other sites of the urinary tract) was observed in a case-control study in which approximate lifetime consumption of paracetamol (whether acute or chronic) was estimated. However, other similar studies have failed to demonstrate statistically significant association between paracetamol and cancer of the urinary tract, or paracetamol and renal cell carcinoma.

There is limited evidence for the carcinogenicity of paracetamol in experimental animals. Liver cell tumours can be detected in mice and liver and bladder carcinomas can be detected in rats, following chronic feeding 500 mg/kg/day paracetamol.

Pseudoephedrine
There is insufficient information available to determine whether pseudoephedrine has carcinogenic potential.

Teratogenicity
Paracetamol
There is no information relating to the teratogenic potential paracetamol. In humans, paracetamol crosses the placenta and attains concentrations in the foetal circulation similar to those in the maternal circulation. Intermittent maternal ingestion of therapeutic doses of paracetamol is not associated with teratogenic effects in humans. Paracetamol has been found to be fetotoxic to cultured rat embryos.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.

Pseudoephedrine
Systemic administration of pseudoephedrine, up to 50 times the human daily dosage in rats and up to 35 times the human daily dosage in rabbits did not produce teratogenic effects.

Fertility
Paracetamol
There is no information relating to the effects of paracetamol on human fertility. A significant decrease in testicular weight was observed when male Sprague-Dawley rats were given daily high doses of paracetamol (500 mg/kg body weight/day) orally for 70 days.

Pseudoephedrine
Systemic administration of pseudoephedrine to rats, up to 7 times the human daily dosage in females and 35 times the human daily dosage in males, did not impair fertility or alter foetal morphological development and survival.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised Maize Starch
Crospovidone (E1202)
Povidone K30 (E1201)
Stearic Acid (E570)
Microcrystalline Cellulose (E460)
Sodium starch glycolate Type A
Magnesium Stearate (E570)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 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 PVC/PVDC/aluminium blisters.
4, 10, 12, 15, 18, 20, 24*, 30 and 32 tablets.
(Maximum pack size in Ireland)*
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/339/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 27th January 2017
Date of Last Renewal: 02nd October 2021

10 DATE OF REVISION OF THE TEXT

September 2022