# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Paralief Extra Film-coated Tablets Paracetamol 500 mg Caffeine 65 mg

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Paracetamol 500 mg and Caffeine 65 mg.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

Capsule-shaped white film-coated tablets.

Size: Approximately 7.0 x 18.25 mm

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Paralief Extra are used for the symptomatic treatment of mild to moderate pain and /or fever.

This medicine is indicated in adults, the elderly and children aged 12 years and over.

### 4.2 Posology and method of administration

**Posology**
Generally, the lowest effective dose should be used, during the shortest time needed to relieve the symptoms.

**Adults and adolescents aged 16 years and over:**
1 to 2 tablets up to four times daily. The dose should not be repeated more frequently than every 4 hours.

Do not exceed 8 tablets in 24 hours.

The maximum daily dose of paracetamol should not exceed 60 mg/kg (up to a maximum of 2g/day) in the following situations, unless directed by a physician:

- Weight less than 50kg
- Hepatocellular insufficiency
- Chronic alcoholism
- Dehydration
- Chronic malnutrition

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

Hepatic Impairment

In patients with hepatic impairment or Gilbert's Syndrome, the dose of paracetamol should be reduced or the dosing interval prolonged. The daily dose of paracetamol should not exceed 2g/day unless directed by a physician.

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:

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

Adolescents aged 12 – 15 years:
One tablet up to four times daily. The dose should not be repeated more frequently than every 4 hours.
The daily dose of paracetamol should not exceed 2g/day.

Children
Not recommended for children under 12 years of age.

If pain persists for more than 5 days or if fever lasts for more than 3 days, or gets worse or other symptoms appear, the patient should stop the treatment and consult a doctor.

Warning: all paracetamol or caffeine containing products, including OTC medicines and food, should be taken into account to prevent overdose (see section 4.4).

Method of administration

For oral administration.

**4.3 Contraindications**

Hypersensitivity to paracetamol, caffeine or to any of the excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**

Contains paracetamol. Do not use with any other paracetamol-containing products. The concomitant use with other products containing paracetamol may lead to an overdose.
Paracetamol overdose may cause liver failure, which can lead to liver transplant or death.
Prolonged or frequent use is discouraged. Prolonged use except under medical supervision may be harmful.

Do not exceed the stated dose. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well because of the risk of delayed, serious liver damage.

Underlying liver disease increases the risk of paracetamol related liver damage. Patients who have been diagnosed with liver or kidney impairment must seek medical advice before taking this medication.

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 of paracetamol should not exceed 2 grams in such cases.

Cases of hepatic dysfunction/failure have been reported in patients with depleted glutathione levels, such as those who are severely malnourished, anorexic, have a low body mass index or are chronic heavy users of alcohol.

Caution in patients with glutathione depleted states such as sepsis; the use of paracetamol may increase the risk of metabolic acidosis.

Caution is advised in asthmatic patients sensitive to acetylsalicylic acid because bronchospastic reactions with paracetamol (cross-reaction) have been reported in less than 5% of the patients tested. If an acute viral hepatitis is diagnosed, the treatment must be stopped. Excessive intake of caffeine (e.g. coffee, tea and some canned drinks) should be avoided while taking this product. Patients should be advised to consult their doctor if their headaches become persistent.

Concomitant use of Paracetamol (4 g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values. In this case, increased monitoring of INR values should be done during the duration of the combination and after its discontinuation.
Interference with laboratory tests: Paracetamol may affect uric acid tests by wolframatop phosphoric acid, and blood sugar tests by glucose-oxydase-peroxydase.

Patients should be advised not to take other paracetamol-containing products concurrently.

Take only when necessary.

In the case of high fever, or signs of secondary infection or persistence of symptoms a doctor should be consulted.

If symptoms persist, consult your doctor.

Keep out of the sight and reach of children.

**Due to the presence of paracetamol:**

• Paralief Extra should be given with care to patients with impaired renal or hepatic function or alcohol dependence.
• The risk of paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicinal products or medicinal products that induce liver microsomal enzymes (e.g. rifampicin, isoniazide, chloramphenicol, hypnotics and antiepileptics including phenobarbital, phenytoin and carbamazepine). Patients with history of alcohol abuse are at special risk of hepatic damage (see section 4.5).
• Patients should be warned not to take other products containing paracetamol concurrently due to the risk of severe liver damage in case of overdose (see section 4.9)
• Alcoholic beverages should be avoided while taking this medicine because alcohol use in combination with paracetamol may cause liver damage (see section 4.5). Paracetamol should be given with caution to patients with alcohol dependence.

**Due to the presence of caffeine:**
• Paralief Extra should be given with care to patients with gout, hyperthyroidism and arrhythmia.
• The patient should limit the use of caffeine containing products when taking Paralief Extra, as excess caffeine may cause nervousness, irritability, sleeplessness and occasionally rapid heartbeat.

**4.5 Interaction with other medicinal products and other forms of interaction**

Paracetamol may increase the elimination half-life of Chloramphenicol. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and decreased by cholestyramine. Oral contraceptives may increase the rate of clearance of paracetamol.

The anticoagulant effect of Warfarin and other Coumarins may be enhanced by prolonged regular daily use of paracetamol with increased risk of bleeding; occasional doses have no significant effect.

**Table 4-1 Paracetamol**

| **Combination of paracetamol with:** | **Possible outcome:** |
|---|---|
| Liver enzyme inducers or potentially hepatotoxic substances (eg., alcohol, rifampicin, isoniazide, hypnotics and antiepileptics including phenobarbital, phenytoin and carbamazepine) | Increased toxicity of paracetamol that could lead to liver damage even with otherwise harmless doses of paracetamol; therefore, liver function should be monitored (see section 4.4). Concomitant use is not recommended. |
| Chloramphenicol | Paracetamol may increase the risk of elevated plasma concentrations of chloramphenicol. Concomitant use is not recommended. |
| Zidovudine | Paracetamol could increase the tendency to develop neutropenia; therefore, the hematological blood monitoring should be performed. Concomitant use is not recommended unless monitored by a doctor. |
| Probenecid | It reduces paracetamol clearance, thus paracetamol doses should be decreased when combined with these agents. Concomitant use is not recommended. |
| Oral anticoagulants | The repeated use of paracetamol for more than one week increases anticoagulant effects. Sporadic doses of paracetamol do not have a significant effect. |
| Propantheline or other agents that lead to slowing of gastric emptying | These agents delay paracetamol absorption; rapid pain relief may be delayed and reduced. |
| Metoclopramide or other agents that lead to acceleration of gastric emptying | These active substances accelerate the paracetamol absorption with increase of the effectiveness and onset of analgesia. |
| Cholestyramin | It reduces paracetamol absorption; therefore cholestyramin should not be given within 1 hour of paracetamol if maximal analgesia is to be achieved. |

**Table 4.2 Caffeine**

| Combination of caffeine with: | Possible outcome: |
|---|---|
| Hypnotic agents (eg., benzodiazepines, barbiturates, antihistamines, etc) | Concomitant use can reduce the hypnotic effect, or antagonize the anticonvulsive effects of barbiturates. Concomitant use is therefore not recommended. If needed, the combination may possibly be more useful in the morning. |
| Lithium | Caffeine withdrawal increases serum lithium since renal clearance of lithium can be increased by caffeine, therefore when caffeine is withdrawn, it may be necessary to reduce the dose of lithium. Concomitant use is therefore not recommended. |
| Disulfiram | Alcoholic patients who are recovering using treatment with disulfiram must be warned to avoid the use of caffeine in order to avoid the risk of alcohol abstinence syndrome worsening due to caffeine-induced cardiovascular and cerebral excitation. |
| Substances of the ephedrine type | Their combination could have an increased dependency potential. Concomitant use is therefore not recommended. |
| Sympathomimetics or levothyroxine | Their combination could have an enhanced tachycardic effect due to synergic effects. Concomitant use is therefore not recommended. |
| Theophylline | Concomitant use could reduce the excretion of theophylline. |
| Antibacterials of the quinolone type (ciprofloxacin, enoxacin, and pipemidic acid), terbinafine, cimetidine, fluvoxamine and oral contraceptives | Increased caffeine half-life due to inhibition of the hepatic cytochrome P - 450 pathway; therefore, patients with hepatic disorders, cardiac arrhythmias or latent epilepsy should avoid taking caffeine. |
| Nicotine, phenytoin and phenylpropanolamine | They decrease the elimination half-life of caffeine. |
| Clozapine | Caffeine increases the serum levels of clozapine due to the probable interaction through both pharmacokinetic and pharmacodynamics mechanisms. Clozapine serum levels should be monitored. |

| | |
|---|---|
| | Concomitant use is therefore not recommended. |

## 4.6 Fertility, pregnancy and lactation

Pregnancy
This product is not recommended for use during 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.

*Caffeine*
Paracetamol-caffeine is not recommended for use during pregnancy due to the possible increased risk of lower birth weight and spontaneous abortion associated with caffeine consumption.
Irritability and poor sleeping pattern in the infant have been reported.

**Breast-feeding**
Paracetamol and caffeine are excreted in breast milk.

***Paracetamol***
Human studies with paracetamol at the recommended doses have not identified any risk to lactation or the breast-fed offspring.

***Caffeine***
Caffeine in breast milk may potentially have a stimulating effect on breast-fed infants.
Due to the caffeine content of this product, it should not be used if you are pregnant or breastfeeding.

**Fertility**
Due to its potential mechanism of action on cyclooxygenase and prostaglandins synthesis, paracetamol could affect women's fertility, through a reversible effect on ovulation.
In animal studies, paracetamol effects on male fertility have been observed. The relevance of this effect in humans is unknown.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable are tabulated below by System organ Class and frequency.

Frequencies are defined as: very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from available data).

Adverse event frequencies have been estimated from spontaneous reports received through post marketing data.

| **Body System** | **Undesirable Effect** | **Frequency** |
|---|---|---|
| **Paracetamol** | | |
| Blood and lymphatic system | Thrombocytopaenia, | Very rare |

| | | |
|---|---|---|
| disorders | Agranulocytosis | |
| Immune System disorders | Anaphylaxis Cutaneous hypersensitivity reactions, including skin reactions, angioedema and Stevens Johnson syndrome /toxic epidermal necrolysis. Very rare cases of serious skin reactions have been reported. | Very rare |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm in patients sensitive to aspirin and other NSAIDs | Very rare |
| Hepatobiliary disorders | Hepatic dysfunction | Very rare |
| **Caffeine** | | |
| Central Nervous System | Nervousness, Dizziness | Not known |

When the recommended paracetamol-caffeine dosing regimen is combined with dietary caffeine intake, the resulting higher dose of caffeine may increase the potential for caffeine-related adverse effects such as insomnia, restlessness, anxiety, irritability, headaches, gastrointestinal disturbances and palpitations.

**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, email: medsafety@hpra.ie.

**4.9 Overdose**

**Paracetamol**
Paracetamol overdose may cause liver failure which can lead to liver transplant or death.
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 risk of liver damage from paracetamol toxicity.
Risk Factors include: 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.
- Regularly consumes ethanol in excess of recommended amounts.
- Is likely to be glutathione deplete e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

***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 >150mg/kg 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.

**Caffeine**
***Symptoms***
Overdose of caffeine may result in epigastric pain, vomiting, diuresis, tachycardia or cardia arrhythmia, CNS stimulation (insomnia, restlessness, excitement, agitation, jitteriness, tremors and convulsions).It must be noted that for clinically significant symptoms of caffeine overdose to occur with this product, the amount ingested would be associated with serious paracetamol-related liver toxicity. No specific antidote is available, but supportive measures such as beta adrencepto antagonists to reverse the cardiotoxic effects may be used.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC code: N02BE51. Paracetamol, combinations excl. psycholeptics
The combination of paracetamol and caffeine is a well-established analgesic combination.

### 5.2 Pharmacokinetic properties

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract.

Paracetamol is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding. Excretion is almost exclusively renal, in the form of conjugated metabolites.

Caffeine is absorbed readily after oral administration. Maximal plasma concentrations are achieved within one hour and the plasma half-life is about 3.5 hours. 65 - 80% of administered caffeine is excreted in the urine as 1-methyluric acid and 1-methylxanthine.

### 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

**Table Core:**
Pregelatinized Starch
Povidone K-30
Crospovidone Type A
Magnesium Stearate

**Film-coat:**
Hypromellose 2910 (E464)
Talc

Titanium dioxide (E171)
Macrogol 400

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

24 months.

**6.4 Special precautions for storage**

Store below 30ºC. Store in the original package in order to protect from light.

**6.5 Nature and contents of container**

PVC/PVDC/Aluminium blisters packed into outer cardboard cartons
or
PVC/Aclar/PVC/Aluminium blisters packed into outer cardboard cartons

Pack sizes: 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 48 or 100 tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

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

**7 MARKETING AUTHORISATION HOLDER**

Chanelle Medical
Dublin Road
Loughrea
Co. Galway

**8 MARKETING AUTHORISATION NUMBER**
PA0688/050/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

June 2018

**10 DATE OF REVISION OF THE TEXT**

September 2019