SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Therimin Honung & Citron 500 mg Powder for Oral Solution

paracetamol

1. NAME OF THE MEDICINAL PRODUCT

Therimin Honung & Citron 500 mg Powder for Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains paracetamol 500 mg.
Excipients with known effect: each sachet also contains aspartame (E951) 31 mg, sodium citrate dihydrate 162 mg (sodium 38 mg), sucrose 4.7 g, Allura Red AC (E129) 0.09 mg, lecithin soya (E322).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution

Off white to pale yellow granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therimin Honung & Citron is indicated for the short-term treatment of painful and/or febrile conditions, such as mild to moderate pain and fever associated with colds and flu, headache, muscles and joints pains, toothache and menstrual pain.

The product is recommended for adults and adolescents aged 12 years and above.

4.2 Posology and method of administration

Posology

Adults:

One to two sachets of powder (500 to 1000 mg) dissolved in hot water every four to six hours as needed, up to 4 times a day. The maximum daily dose is 6 sachets in 24 hours (paracetamol 3000 mg per 24 hours). Usually one sachet per dose is sufficient.

The total dose of paracetamol should not exceed 60 mg/kg/day for adolescents and adults weighing less than 50 kg.

Do not exceed the stated dose.

The lowest dose necessary to achieve efficacy should be used for the shortest duration of treatment.

Paediatric population:

Doses depend on age and body weight. A single dose ranges from 10 to 15 mg/kg body weight. The maximum total daily dose is 60 mg/kg body weight.

- Children below 12 years of age: this product is not recommended in children aged less than 12 years.
- Adolescents of 12 to 15 years and weighing 41 to 50 kg: one sachet per dose, every four to six hours as needed, up to four times a day. The maximum dose is 4 sachets in 24 hours (paracetamol 2000 mg per 24 hours).
- Adolescents of 16 to 18 years and weighing more than 50 kg: as adults.

Higher doses than those recommended can result in very severe liver damage.

If pain persists for more than 5 days or fever lasts for more than 3 days, or worsen, a physician should be consulted.

Hepatic Impairment

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

Renal Impairment

In patients with renal insufficiency, the dose should be reduced, and the dosing interval should be increased to 6 hours.

Elderly patients

Dose adjustment is not required in the elderly.

Method of administration

The contents of 1 or 2 sachets should be dissolved in a standard mug of hot, but not boiling, water (approximately 250 ml). When 2 sachets are used, more water can be added according to taste. Drink when cooled to an acceptable temperature.

For appearance of the medicinal product after dissolution of the powder, see section 6.6

4.3 Contraindications

- Hypersensitivity to paracetamol or to any of the excipients listed in section 6.1.
- Allergy to peanut or soya, due to presence of soya lecithin.

4.4 Special warnings and precautions for use

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.

Caution should be exercised in patients with asthma who are sensitive to acetylsalicylic acid, as mild reactions of bronchospasm have been reported with paracetamol (cross-reaction).

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 monitoringis 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.

Patients should be advised not to take any other paracetamol-containing products concurrently due to the risk of severe liver damage or liver failure which may require liver transplant or lead to death in case of overdose (see section 4.9).

Alcoholic beverages should be avoided while taking this product because concomitant use of paracetamol may cause liver damage. Paracetamol should be given with caution to patients with alcohol dependence.

Information concerning excipients

This medicine contains:

- Aspartame (E951) 31 mg per sachet a source of phenylalanine, which may be harmful for patients with phenylketonuria.
- Sodium 38 mg per sachet: equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
- Sucrose 4.7 g per sachet: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This should also be taken into account in patients with diabetes mellitus.
- Allura red AC (E129) 0.09 mg per sachet: an azo colouring agent, it may cause allergic reactions.
- Lecithin soya (E322). If you are allergic to peanut or soya, do not use this medicinal product.

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.

Pharmacokinetic interactions:

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

Concurrent intake of medicines that slow gastric emptying can delay the absorption and onset of effect 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 due to pyroglutamic acidosis, especially in patients with risk factors (see section 4.4).

Cholestyramine reduces the absorption of paracetamol. Cholestyramine should not be given within one hour of administration of paracetamol in order to achieve maximum analgesic effect.

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

Probenecid inhibits the binding of paracetamol to glucuronic acid, thus leading to a reduction in paracetamol clearance by a factor of approximately 2. In patients concurrently taking probenecid, the paracetamol dose should be reduced.

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.

Paracetamol may affect the pharmacokinetic of chloramphenicol. Monitoring of chloramphenicol plasma levels is recommended if combining paracetamol with chloramphenicol injection treatment.

4.6 Pregnancy and lactation

Pregnancy
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.

During pregnancy, paracetamol should not be taken for a long period, at high doses or in combination with other medicinal products, as safety of use has not been established in such cases.

Breast-feeding
Paracetamol is excreted in small amounts into breast milk. However, at therapeutic doses of paracetamol no effects on the suckling child are anticipated. Paracetamol can be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Therimin Honung & Citron has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: *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).

System Organ Class	**Rare** **(≥ 1/10,000 to < 1/1,000)**	**Very rare** **(< 1/10,000)**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders	Platelet disorders, stem cell disorders, agranulocytosis, leucopenia, thrombocytopenia, haemolytic anaemia, pancytopenia		
Immune system disorders	Allergies (excluding angioedema)	Anaphylaxis	
Psychiatric disorders	Depression, confusion, hallucinations		
Nervous system disorders	Tremor, headache		
Eye disorders	Abnormal vision		
Cardiac disorders	Oedema		
Gastrointestinal disorders	Haemorrhage, abdominal pain, diarrhoea, nausea, vomiting		
Hepato-biliary disorders	Abnormal hepatic function, hepatic failure, hepatic necrosis, jaundice.	Hepatotoxicity	
Skin and subcutaneous tissue disorders	Pruritus, rash, sweating, purpura, angioedema, urticaria	Cutaneous hypersensitivity reactions including, among others, Stevens Johnson syndrome and Toxic Epidermal Necrolysis	
General disorders and administration site conditions	Dizziness (excluding vertigo), malaise, pyrexia, sedation		
Respiratory, thoracic and mediastinal disorders		Bronchospasm in patients sensitive to aspirin and other NSAIDs	

General disorders and administration site conditions		Hypersensitivity reaction (requiring discontinuation of treatment)	
Metabolism and nutrition disorders		Hypoglycemia	High anion gap metabolic acidosis
Renal and urinary disorders		Sterile pyuria (cloudy urine) and renal side effects	

Description of selected adverse reactions

Very rare cases of serious skin reactions have been reported. Interstitial nephritis has been reported incidentally after prolonged use of high doses. Some cases of epidermal necrolysis, Steven Johnson syndrome, erythema multiforme, edema of the larynx, anaphylactic shock, anemia, liver alteration and hepatitis, renal alteration (severe renal impairment, haematuria, anuresis), gastrointestinal effects and vertigo have been reported.

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 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 listed in Appendix V

4.9 Overdose

In an acute overdose, paracetamol may exert a hepatotoxic effect or even cause necrosis of the liver. Overdose may cause liver failure which may require liver transplant or lead to death. Acute pancreatitis has been observed, usually with hepatic dysfunction and liver toxicity. Overdose of paracetamol, including high total dose levels reached over a prolonged period, may cause analgesic induced nephropathy with irreversible liver failure. Patients should be warned not to take other products containing paracetamol concurrently.

There is a risk of poisoning, particularly in elderly subjects, in young children, in patients with liver disease, in cases of chronic alcoholism and in patients with chronic malnutrition. Overdose of paracetamol is potentially fatal in all populations.

Symptoms

Symptoms of paracetamol overdose in the first 24 hours are pallor, nausea, vomiting, and anorexia. Abdominal pain may be the first indication of liver damage, which is not usually apparent for 24 to 48 hours and sometimes may be delayed for up to 4 to 6 days after ingestion. Liver damage is generally at a maximum 72 to 96 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Acute renal failure with acute tubular necrosis may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management

Immediate treatment is essential in the management of paracetamol overdose even if symptoms of overdose are not present. Early administration of N-acetylcysteine i.v. or per os as an antidote to paracetamol, possibly gastric lavage and/or administration of oral methionine, may have beneficial effect up to at least 48 hours after the overdose. Administration of activated charcoal and monitoring of breathing and circulation may be useful. In cases of convulsions, diazepam may be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other analgesic and antipyretics; anilides.

ATC code: N02BE01

Paracetamol has analgesic and antipyretic properties. It is used for the relief of mild to moderate pain and for fever. The primary mechanism of action may be the inhibition of prostaglandins synthesis. Paracetamol produces peripheral vasodilation yielding increased blood flow through the skin, perspiration and heat loss.

The analgesic effect starts within 30 minutes, with maximum effect within 1 to 2 hours and lasts up to 4 to 5 hours. The antipyretic effect starts within 30 to 60 minutes. The maximum antipyretic effect is between 2 to 3 hours and the effect lasts up to 8 hours.

Unlike acetyl salicylic acid, paracetamol does not cause gastrointestinal irritation and is well tolerated by patients. Thrombocyte aggregation and bleeding time are generally not affected by paracetamol. Patients with hypersensitivity to acetyl salicylic acid generally tolerate paracetamol.

5.2 Pharmacokinetic properties

Absorption
Paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma concentration occurs after 30 to 60 minutes.

Distribution
Paracetamol is distributed rapidly into all tissues. Blood, plasma and saliva concentrations are comparable. Protein binding is low with recommended doses.

Biotransformation
Paracetamol is mainly metabolised in the liver in 2 major ways: conjugation with glucuronic acid and sulphuric acid. At doses that exceed the therapeutic dose, the latter route is rapidly saturated. A lesser fraction of metabolism occurs via the catalysator, cytochrome P450 (mainly CYP2E1) and leads to the formation of the metabolite N-acetyl-p-benzoquinone imine, which is normally rapidly detoxified by glutathione and bound by cysteine and mercapturic acid. In the event of massive overdose, the quantity of this toxic metabolite is increased.

Elimination
Elimination is mainly in the urine. 90% of the absorbed amount is renally excreted within 24 hours, mainly as glucuronides (60–80%) and sulphate conjugates (20–30%). Less than 5% is eliminated in unchanged form. The elimination half-life is approximately 2 hours.

Renal insufficiency
In patients with severe renal insufficiency (creatinine clearance <10 ml/min), elimination of paracetamol and its metabolites is delayed.

Elderly patients
Conjugation is unchanged in this patient group.

5.3 Preclinical safety data

The preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, teratogenicity, genotoxicity, or carcinogenic potential. Overdose may lead to serious hepatotoxicity.

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available. Non-clinical safety data for paracetamol have not revealed findings that are of relevance to the recommended dosage and use of the product.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid (Vitamin C)
Acesulfame potassium
Aspartame (E951)
Calcium phosphate
Citric acid
Maltodextrin
Silica, colloidal hydrated
Sodium citrate
Sucrose
Quinoline yellow (E104)
Brilliant blue FCF (E133)
Allura red AC (E129)
Lemon flavour (contains lecithin soya (E322))
Chamomile flavour (contains lecithin soya (E322))
Honey flavour (contains lecithin soya (E322))
White tea flavour.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The product is packed in unit dose sachet made of polyethylene terephthalate/low density polyethylene/aluminium foil/low density polyethylene heat seal coating.

Packs of 6, 8, 10 or 12 sachets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

After dissolution of the powder in hot water, the liquid has a hazy yellow to brownish yellow colour.

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: <{DD month YYYY}>

Date of last renewal: <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

24-OCT-2025