

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Rupatadine 10 mg tablets

Zealargy

2. Qualitative and quantitative composition

Each tablet contains 10 mg of rupatadine.

Excipient with known effect

Each tablet also contains 60 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Salmon-coloured, round-shaped, biconvex, plain tablet.

4. Clinical particulars

4.1 Therapeutic indications

Symptomatic treatment of allergic rhinitis and urticaria in adults and adolescents (over 12 years of age).

4.2 Posology and method of administration

Posology

Adults and adolescents (over 12 years of age)

The recommended dose is 10 mg (one tablet) once a day, with or without food.

Elderly

Rupatadine should be used with caution in elderly people (see section 4.4).

Paediatric patients

Rupatadine is not recommended for use in children below age 12. In children aged 2 to 11 years, the administration of rupatadine 1 mg/ml oral solution is recommended.

Patients with renal or hepatic insufficiency

As there is no clinical experience in patients with impaired kidney or liver functions, the use of rupatadine is at present not recommended in these patients.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

The administration of rupatadine with grapefruit juice is not recommended (see section 4.5).

The combination of rupatadine with potent CYP3A4 inhibitors should be avoided and moderate CYP3A4 inhibitors should be administered with caution (see section 4.5).

Dose adjustment of sensitive CYP3A4 substrates (e.g., simvastatin, lovastatin) and CYP3A4 substrates with a narrow therapeutic index (e.g., ciclosporin, tacrolimus, sirolimus, everolimus, cisapride) could be required as rupatadine may increase plasma concentrations of these drugs (see section 4.5).

Cardiac safety of rupatadine was assessed in a Thorough QT/QTc study. Rupatadine up to 10 times the therapeutic dose did not produce any effect on the ECG and hence raises no cardiac safety concerns. However, rupatadine should be used with caution in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia.

Rupatadine should be used with caution in elderly patients (65 years and older). Although no overall differences in effectiveness or safety were observed in clinical trials, the higher sensitivity of some older individuals cannot be excluded due to the low number of elderly patients enrolled (see section 5.2).

Regarding use in children less than 12 years old and patients with renal or hepatic impairment, see section 4.2.

Excipients

This medicine contains **lactose**. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration with potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, nefazodone) should be avoided and co-medication with moderate CYP3A4 inhibitors (erythromycin, fluconazole, diltiazem) should be used with caution.

The concomitant administration of rupatadine 20 mg and ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2-3 times respectively. These modifications were not associated with an effect on the QT interval or with an increase in adverse reactions in comparison with the drugs when administered separately.

Interaction with grapefruit: The concomitant administration of grapefruit juice increased 3.5 times the systemic exposure of rupatadine. Grapefruit juice should not be taken simultaneously.

Effects of rupatadine on other drugs

Caution should be taken when rupatadine is co-administered with other metabolised drugs with

narrow therapeutic windows since knowledge of the effect of rupatadine on other drugs is limited.

Interaction with alcohol: After administration of alcohol, a dose of 10 mg of rupatadine produced marginal effects in some psychomotor performance tests although they were not significantly different from those induced by intake of alcohol only. A dose of 20 mg increased the impairment caused by the intake of alcohol.

Interaction with CNS depressants: As with other antihistamines, interactions with CNS depressants cannot be excluded.

Interaction with statins: Asymptomatic CPK increases have been uncommonly reported in rupatadine clinical trials. The risk of interactions with statins, some of which are also metabolised by the cytochrome P450 CYP3A4 isoenzyme, is unknown. For these reasons, rupatadine should be used with caution when it is coadministered with statins.

4.6 Pregnancy and lactation

Pregnancy

There is a limited amount of data on the use of rupatadine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of rupatadine during pregnancy.

Breastfeeding

Rupatadine is excreted in animal milk. It is unknown whether rupatadine is excreted into breast milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from rupatadine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There is no clinical data on fertility. Studies in animals have shown a significant reduction of fertility at exposure levels higher than those observed in humans at the maximum therapeutic dose (see section 5.3).

4.7 Effects on the ability to drive and use machines

Rupatadine has no influence on the ability to drive and use machines. Nevertheless, care should be taken before driving or using machinery until the patient's reaction to rupatadine has been established.

4.8 Undesirable effects

Rupatadine has been administered to over 2025 adult and adolescent patients in clinical studies, 120 of whom received rupatadine for at least 1 year.

The most common adverse reactions in controlled clinical studies were somnolence (9,5%), headache (6,9%) and fatigue (3,2%)

The majority of the adverse reactions observed in clinical trials were mild to moderate in severity

and they usually did not require cessation of therapy.

The frequencies of adverse reactions are assigned as follows:

- *Common* ($\geq 1/100$ to $< 1/10$)
- *Uncommon* ($\geq 1/1000$ to $< 1/100$)
- *Rare* ($\geq 1/10,000$ to $< 1/1,000$)

The frequencies of adverse reactions reported in patients treated with rupatadine during clinical trials and spontaneous reporting were as follows:

Infections and infestations

- *Uncommon*: Pharyngitis, Rhinitis

Immune system disorders

- *Rare*: Hypersensitivity reactions (including anaphylactic reactions, angioedema and urticaria)*

Metabolism and nutrition disorders

- *Uncommon*: Increased appetite

Nervous system disorders

- *Common*: Somnolence, Headache, Dizziness
- *Uncommon*: Disturbance in attention

Cardiac disorders

- *Rare*: tachycardia and palpitations*

Respiratory, thoracic, and mediastinal disorders

- *Uncommon*: Epistaxis, Nasal dryness, Cough, Dry throat, Oropharyngeal pain

Gastrointestinal disorders

- *Common*: Dry mouth
- *Uncommon*: Nausea, Abdominal pain upper, Diarrhoea, Dyspepsia, Vomiting, Abdominal pain, Constipation

Skin and subcutaneous tissue disorders

- *Uncommon*: Rash

Musculoskeletal, connective tissues, and bone disorders

- *Uncommon*: Back pain, Arthralgia, Myalgia

General Disorders and administration site condition

- *Common*: Fatigue, Asthenia
- *Uncommon*: Thirst, Malaise, Pyrexia, Irritability

Investigations

- *Uncommon*: Blood creatine phosphokinase increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Liver function test abnormal, Weight increased

* tachycardia and palpitations and hypersensitivity reactions (including anaphylactic reactions, angioedema and urticarial) have been reported in post-marketing experience with rupatadine.

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 e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search

for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose

No case of overdose has been reported. In a clinical safety study rupatadine at a daily dose of 100 mg for 6 days was well tolerated. The most common adverse reaction was somnolence. If accidental ingestion of very high doses occurs symptomatic treatment together with the required supportive measures should be given.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 5 Antihistamines.

Rupatadine is a second-generation antihistamine, a long-acting histamine antagonist, with selective peripheral H₁-receptor antagonist activity. Some of the metabolites (desloratadine and its hydroxylated metabolites) retain an antihistaminic activity and may partially contribute to the overall efficacy of the drug.

In vitro studies with rupatadine at high concentrations have shown an inhibition of the degranulation of mast cells induced by immunological and non-immunological stimuli as well as the release of cytokines, particularly of the TNF_α in human mast cells and monocytes. The clinical relevance of the observed experimental data remains to be confirmed.

Clinical trials in volunteers (n=375) and patients (n=2650) with allergic rhinitis and chronic idiopathic urticaria did not show a significant effect on the electrocardiogram when rupatadine was administered at doses ranging from 2 mg to 100 mg.

Chronic idiopathic urticaria was studied as a clinical model for urticarial conditions, since the underlying pathophysiology is similar, regardless of aetiology, and because chronic patients can be more easily recruited prospectively. Since histamine release is a causal factor in all urticarial diseases, rupatadine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria, as advised in clinical guidelines.

In placebo-controlled trials in patients with Chronic Idiopathic Urticaria, rupatadine was effective in reducing the mean pruritus score from baseline over the 4-week treatment period (change vs baseline: rupatadine 57.5%, placebo 44.9%) and decreasing the mean number of wheals (54.3% vs 39.7%).

5.2 Pharmacokinetic properties

Absorption and bioavailability

Rupatadine is rapidly absorbed after oral administration, with a T_{max} of approximately 0.75 hours after intake. The mean C_{max} was 2.6 ng/ml after a single oral dose of 10 mg and 4.6 ng/ml after a single oral dose of 20 mg. Pharmacokinetics of rupatadine was linear for a dose between 10 and 20 mg after single and repeated doses. After a dose of 10 mg once a day for 7 days, the mean C_{max} was

3.8 ng/ml. The plasma concentration followed a bi-exponential drop-off with a mean elimination half-life of 5.9 hours. The binding rate of rupatadine to plasma proteins was 98.5-99%.

As rupatadine has never been administered to humans by intravenous route, no data is available on its absolute bioavailability.

Effect of the intake of food

Intake of food increased the systemic exposure (AUC) to rupatadine by about 23%. The exposure to one of its active metabolites and the main inactive metabolite was practically the same (reduction of about 5% and 3% respectively). The time taken to reach the maximum plasma concentration (t_{\max}) of rupatadine was delayed by 1 hour. The maximum plasma concentration (C_{\max}) was not affected by food intake. These differences had no clinical significance.

Metabolism and elimination

In a study of excretion in humans (40 mg of ^{14}C -rupatadine), 34.6% of the radioactivity administered was recovered in urine and 60.9% in faeces collected over 7 days. Rupatadine undergoes considerable pre-systemic metabolism when administered by oral route. The amounts of unaltered active substances found in urine and faeces were insignificant. This means that rupatadine is almost completely metabolised. Roughly, the active metabolites desloratadine and other hydroxylated derivatives accounted for 27% and 48%, respectively, of the total systemic exposure of the active substances. *In vitro* metabolism studies in human liver microsomes indicate that rupatadine is mainly metabolised by the cytochrome P450 (CYP 3A4).

Specific patient groups

In a study on healthy volunteers to compare the results in young adults and elderly patients, the values for AUC and C_{\max} for rupatadine were higher in the elderly than in young adults. This is probably due to a decrease in the first-pass hepatic metabolism in the elderly. These differences were not observed in the metabolites analysed. The mean elimination half-life of rupatadine in elderly and young volunteers was 8.7 hours and 5.9 hours respectively. As these results for rupatadine and its metabolites were not clinically significant, it was concluded that it is not necessary to make any adjustments when using a dose of 10 mg in the elderly.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

More than 100 times the clinically recommended dose (10 mg) of rupatadine did neither extend the QTc or QRS interval nor produce arrhythmia in various species of animals such as rats, guinea pigs and dogs. Rupatadine and one of its main active metabolites in humans, 3-hydroxydesloratadine, did not affect the cardiac action potential in isolated dog Purkinje fibres at concentrations at least 2000 times greater than the C_{\max} reached after the administration of a dose of 10 mg in humans. In a study that evaluated the effect on cloned human HERG channel, rupatadine inhibited that channel at a concentration 1685 times greater than the C_{\max} obtained after the administration of 10 mg of rupatadine. Desloratadine, the metabolite with the greatest activity, had no effect at a 10-micromolar concentration. Studies of tissue distribution in rats with radiolabelled rupatadine showed that

rupatadine does not accumulate in heart tissue.

In the rat, a significant reduction of male and female fertility occurred at the high dose of 120 mg/kg/day, providing C_{\max} 268 times those measured in humans at the therapeutic dose (10 mg/day). Foetal toxicity (growth delay, incomplete ossification, minor skeletal findings) was reported in rats at maternotoxic dose levels only (25 and 120 mg/kg/day). In rabbits, no evidence of developmental toxicity was noted at doses up to 100 mg/kg. The developmental No Adverse Effect Levels were determined at 5 mg/kg/day in rats and 100 mg/kg/day in rabbits, yielding C_{\max} 45 and 116 times higher, respectively, than those measured in humans at the therapeutic dose (10 mg/day).

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Pregelatinized starch
Iron oxide red
Iron oxide yellow
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C. Keep the blister in the outer carton to protect it from light.

6.5 Nature and contents of the container

The tablets are packed in PVC/PVDC/Alu foil packs.

Pack sizes: 1 x 10 tablets, 2 x 10 tablets and 3 x 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and handling

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

7. APPLICANT

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8. MANUFACTURERS

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9. REGISTRATION DETAILS

Zimbabwe registration number: 2023/5/6464
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10. DATE OF REVISION OF TEXT

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