PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Rupafin 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
10 mg of rupatadine (as fumarate)
Excipients: lactose 57.57 mg as lactose monohydrate
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Round, light salmon coloured tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Adults and adolescents (12 years of age and above)
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 10 mg Tablets is not recommended for use in children below age 12 due to a lack of data on safety and efficacy.

Patients with renal or hepatic insufficiency
As there is no clinical experience in patients with impaired kidney or liver functions, the use of Rupatadine 10 mg Tablets is at present not recommended in these patients.

4.3 Contraindications

Hypersensitivity to rupatadine or to any of the excipients.

4.4 Special warnings and precautions for use

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

Cardiac safety of rupatadine was assessed in a Thorough QT/QTc study. Rupatadine up to 10 times 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 10 mg Tablets 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, 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 in patients with renal or hepatic impairment, see section 4.2.

Due to the presence of lactose monohydrate in rupatadine 10 mg tablets, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with ketoconazole or erythromycin: 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 of the adverse reactions in comparison with the drugs when administered separately. However**,** rupatadine should be used with caution when it is administered concomitanly with these drug substances and other inhibitors of the isozyme CYP3A4.

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.

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

Data on a limited number (2) exposed pregnancies indicate no adverse effects of rupatadine on pregnancy or on the health of the foetus/newborn child. To date, no other

relevant epidemiological data are available. 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). Caution should be exercised when prescribing rupatadine to pregnant women.

Rupatadine is excreted in animal milk. It is unknown whether rupatadine is excreted into breast milk. Due to the lack of human data, caution should be exercised when prescribing rupatadine to lactating women.

4.7 Effects on the ability to drive and use machines

Rupatadine 10 mg had no influence on the ability to drive and use machines. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction on rupatadine has been established.

4.8 Undesirable effects

Rupatadine 10 mg has been administered to over 2025 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 adverse reactions observed in clinical trials were mild to moderate in severity and usually did not require cessation of therapy. The frequencies are summarised according to the following scheme:

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)
Investigations		Blood creatine phosphokinase increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Liver function test abnormal, Weight increased
Nervous system disorders	Somnolence, Headache, Dizziness	Disturbance in attention
Respiratory, thoracic and mediastinal disorders		Epistaxis, Nasal dryness, Pharyngitis, Cough, Dry throat, Pharyngolaryngeal pain, Rhinitis
Gastrointestinal disorders	Dry mouth	Nausea, Abdominal pain upper, Diarrhoea, Dyspepsia, Vomiting, Abdominal pain, Constipation
Skin and subcutaneous tissue disorders		Rash

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)
Musculoskeletal and connective tissue disorders		Back pain, Arthralgia, Myalgia
Metabolism and nutrition disorders		Increased appetite
General disorders and administration site conditions	Fatigue, Asthenia	Thirst, Malaise, Pyrexia
Psychiatric disorders		Irritability

4.9 Overdose

No case of overdose has been reported. In a clinical safety study rupatadine at daily dose of 100 mg during 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

Pharmacotherapeutic group: other antihistamines for systemic use, ATC code: R06A X28.

Rupatadine is a second generation antihistamine, long-acting histamine antagonist, with selective peripheral H_1-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 concentration 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 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 etiology, 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 a placebo-controlled trials in patients with Chronic Idiopathic Urticaria, rupatadine was effective 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 40 mg. 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 to 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 substance found in urine and faeces were insignificant. This means that rupatadine is almost completely metabolised. *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 of 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 for its metabolites were not clinically significant, it was concluded that it is not necessary to make any adjustment 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

Pregelatinised maize-starch
Microcrystalline cellulose
Red iron oxide (E-172)
Yellow iron oxide (E-172)
Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light. Store below 30ºC.

6.5 Nature and content of the container

PVC/PVDC/aluminium blister.
Pack of 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local

requirements.

7. NAME AND ADDRESS OF MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

5 December 2022