PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

RUPAGEX 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Rupatadine (equivalent to Rupatadine fumarate) 10 mg

Contains sugar: lactose monohydrate 38.00 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Light-salmon round 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

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 population

Rupagex is not recommended for use in children below age 12, see section 4.4.

Patients with renal or hepatic insufficiency

As there is no clinical experience in patients with impaired kidney or liver functions, the use of Rupagex is not recommended in these patients, see section 4.4.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Rupagex is not recommended for use in children below 12 years of age.

Pregnancy and lactation

4.4 Special warnings and precautions for use

Renal and hepatic impairment:

Patients with impaired kidney or liver functions, the use of Rupagex is not recommended in these patients (see section 4.2).

Paediatric patients:

Rupagex is not recommended for use in children under 12 years as safety is not established (see sections 4.2 and 4.3).

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

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

Rupagex should be used with caution in patients with known prolongation of the QT interval, patients with uncorrected hypokalaemia, patients with ongoing prodysrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia.

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

Contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance, total 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.

Interactions with ketoconazole or erythromycin:

The concomitant administration of Rupagex and ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2 – 3 times respectively. Caution is recommended in case of concomitant administration of rupatadine and these medicines or other CYP3A4 isoenzyme inhibitors (see section 4.4).

Interaction with grapefruit:

The concomitant administration of grapefruit juice with Rupagex increased the systemic exposure of rupatadine by 3,5 times. It is recommended to avoid intake of grapefruit juice along with Rupagex.

Interaction with alcohol:

Rupagex should be used with caution when administered with alcohol.

Interaction with CNS depressants:

Interactions with other CNS depressants has not been established. No interactions have been observed with fluoxetine.

Interaction with statins:

Asymptomatic CPK increases have been uncommonly reported in rupatadine. The risk of interactions with statins, some of which are also metabolised by the cytochrome P450 CYP3A4 isoenzyme, is unknown. Rupatadine should be used with caution when it is co-administered with statins.

4.6 Fertility, pregnancy and lactation

Pregnancy

H_1 antihistamines cross the placenta.

The use of Rupagex in pregnancy is contraindicated (see section 4.3).

Breastfeeding

Rupagex is excreted in animal milk.

Due to potential harmful effects in neonates, the use of Rupagex is contraindicated during breastfeeding (see section 4.3).

Fertility

There are 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.

4.7 Effects on ability to drive and use machines

This medicine lacks significant sedative effects.

At the recommended dosage, Rupagex is not expected to have an effect on the ability to drive and use machines. Nevertheless, caution is recommended before driving or using a machine until the patient's individual reaction to rupatadine has been determined.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent adverse reactions are somnolence, headache and fatigue.
The majority of adverse reactions observed were mild to moderate in severity and usually did not require cessation of therapy.

b. Tabulated list of adverse reactions presented in system organ class and frequency

System organ class	Undesirable effect	Frequency
Infections and Infestations	Pharyngitis, Rhinitis	Less Frequent
Metabolism and nutrition disorders	Increase appetite	Less Frequent
Psychiatric disorders	Irritability	Less Frequent
Nervous system Disorders	Dizziness Headache Somnolence Disturbance in Attention	Frequent Less Frequent
Cardiac disorders	Tachycardia, palpitations	Less frequent
Respiratory, thoracic and mediastinal disorders	Cough, Dry Throat Epistaxis, Nasal Dryness, Oropharyngeal Pain, Upper respiratory disorders	Less Frequent

Gastrointestinal Disorders	Dry Mouth Abdominal Pain, Upper Abdominal Pain, Diarrhoea, Dyspepsia, Nausea, Vomiting, Constipation	Frequent Less Frequent
Skin and subcutaneous tissue disorders	Rash	Less Frequent
Musculoskeletal, connective tissues, and bone disorders	Arthralgia, Back Pain, Myalgia	Less Frequent
General disorders and administration site conditions	Asthenia, Fatigue Malaise, Pyrexia, Thirst	Frequent Less Frequent

Investigations	Alanine aminotransferase, Increased Aspartate aminotransferase, Increased Blood Creatine Phosphokinase, Increased Liver Function Test Abnormal, Weight increase	Less Frequent

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

May also report to Adcock Ingram Limited using the following email:

Adcock.AEReports@adcock.com

4.9 Overdose

Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.7.1 Antihistaminics.

Pharmacotherapeutic group: other antihistamines for systemic use

ATC Code: R06A X28

Mechanism of action

Rupatadine is a non-sedating, long-acting histamine antagonist, with selective peripheral H1-receptors. At the recommended dose of 10 mg, the onset of the antihistamine activity was at 30 minutes and the effect lasted for 24 hours.

Some of the metabolites (desloratadine and its hydroxylated metabolites) retain an antihistaminic activity and may partially contribute to the overall efficacy of the rupatadine.

Rupatadine possesses antihistamine properties such as the inhibition of the degranulation of mast cells induced by immunological and nonimmunological stimuli, and inhibition of the release of cytokines particularly of the TNFa in human mast cells and monocytes.

Rupatadine shows high H1-receptor affinity and little or no activity on other CNS receptors.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Rupatadine is rapidly absorbed after oral administration. The time taken to reach plasma concentration (T_{max}) was 0.75-1.0 hour (median values). The mean C_{max} is 2,6 ng/ml after a single oral dose of 10 mg. After the administration of a 10 mg dose once a day for 7 days, the mean C_{max} was 3,8 ng/ml. The plasma concentration exhibited a bi-exponential drop-off with a mean elimination half-life of 5.9 hours.

Effects of food intake

The 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 one hour. The maximum plasma concentration (C_{max}) was not affected by food intake. These differences had no clinical significance.

Distribution

Although rupatadine is 98-99% bound to human plasma proteins, it is well distributed in other tissues indicating that this high degree of binding does not cause the compound to be retained in circulating blood allowing it to reach its target receptors. Its plasma concentration is lower than would be expected to saturate plasma binding capacity; hence rupatadine displacement from its binding sites when co-administered with other medicines is unlikely.

Biotransformation

The main biotransformation pathways of rupatadine identified were different oxidative processes, namely oxidation of the pyridine methyl group to the carboxylic acid, hydroxylation in the 3, 5 and 6 positions in the tricyclic ring system and N-dealkylation of the piperadine nitrogen. Conjugates with glucuronic acid were also found. Some of the metabolites retain antihistaminic activity and may partially contribute to the overall efficacy of rupatadine and a long duration of action.

CYP3A4 was identified in vitro as the main isoenzyme responsible for the biotransformation of rupatadine and a genetic polymorphism in its biotransformation is unlikely.

Elimination

The plasma concentration follows a bi-exponential drop with a mean elimination $T_{1/2}$ of 5,9 hours. In a study on humans using radio-labelled rupatadine (^{14}C-rupatadine 40 mg), 34,6 % of the radio-activity administered was recovered in urine and 60,9 % in faeces collected over 7 days.

Biliary excretion is the most important route of elimination Rupatadine undergoes considerable pre-systemic metabolism when administered by orally, and hence the amounts of unaltered active substance found in faeces and urine are very low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Magnesium stearate

Microcrystalline cellulose PH 102

Pregelatinized starch (Maize)

Red Iron oxide E172

Yellow Iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep blisters in outer carton until required for use.

6.5 Nature and contents of container

Packed into thermoformed blisters made of silver Aluminum (25 µm) and PVC (250 µm)/PVdC clear film (40 g/m^2).

Pack sizes: 1x10, 2x10 and 3x10 blisters.

Blisters are packed in a cardboard carton.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

53/5.7.1/0724

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 July 2024

10. DATE OF REVISION OF THE TEXT

30 July 2024