SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

RUPANASE 10, Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is rupatadine fumarate 12,80 mg equivalent to rupatadine 10 mg base.

Contains sugar. Each tablet contains lactose monohydrate 61,100 mg per tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

RUPANASE 10 tablets are round, biconvex, light salmon pink in colour with no markings.

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.

Special populations

Elderly:

RUPANASE 10 should be used with caution in elderly people (see section 4.4).

Paediatric population

RUPANASE 10 is not recommended for use in children below 12 years of age (see section 4.3).

Method of administration

Oral use.

RUPANASE 10 can be taken with or without food.

4.3 Contraindications

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

RUPANASE 10 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

As there is no clinical experience in patients with impaired kidney or liver functions, the use of RUPANASE 10 is not recommended in these patients.

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

The combination of RUPANASE 10 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 RUPANASE 10 may increase plasma concentrations of these drugs (see section 4.5).

Cardiac Safety

RUPANASE 10 should be used with caution in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, patients with ongoing prodysrhythmic conditions, such as clinically significant bradycardia and acute myocardial ischaemia.

Use in the elderly

RUPANASE 10 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.

Excipients with known effect

Due to the presence of lactose monohydrate, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take RUPANASE 10.

Paediatric population

RUPANASE 10 is not recommended for use in children under 12 years as safety is not established.

4.5 Interactions with other medicines and other forms of interactions.

Effects of other medicine on RUPANASE 10

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 RUPANASE 10 and ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2-3 times respectively.

Interaction with grapefruit: The concomitant administration of grapefruit juice with RUPANASE 10 increased the systemic exposure of rupatadine by 3,5 times. It is recommended to avoid intake of grapefruit juice along with RUPANASE 10.

Effects of RUPANASE 10 on other medicine

Caution should be taken when RUPANASE 10 is co-administered with other metabolised medicine with narrow therapeutic windows since knowledge of the effect of RUPANASE 10 on other medicine is limited.

Interaction with alcohol: RUPANASE 10 should be used with caution when administered with alcohol. After administration of alcohol, a dose of RUPANASE 10 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: Interactions with other CNS depressants has not been established. No interactions have been observed with fluoxetine.

Interaction with statins: Asymptomatic CPK increases have been reported in RUPANASE 10 clinical trials. The risk of interactions with statins, some of which are also metabolized by the cytochrome P450 CYPA4 isoenzyme, is unknown. RUPANASE 10 should be used with caution when co-administered with statins.

Interaction with midazolam: After the administration of RUPANASE 10 in combination with 7,5 mg midazolam, an increase of exposure (C_{max} and AUC) of midazolam was mildly higher observed. For this reason, RUPANASE 10 acts as a mild inhibitor of CYP3A4.

4.6 Fertility, pregnancy and lactation

Pregnancy

RUPANASE 10 is contraindicated.

Breastfeeding

RUPANASE 10 is excreted in animal milk. Due to potential harmful effects in neonates, the use of RUPANASE 10 should be avoided during breastfeeding.

4.7 Effects on ability to drive and use machines

At the recommended dosage, RUPANASE 10 is not expected to influence the ability to drive or use machinery. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction to RUPANASE 10 has been established.

4.8 Undesirable effects

System Organ Class	**Common** **(≥ 1/100 to < 1/10)**	**Uncommon** **(≥ 1/1000 to < 1/100)**
Infections and infestations		Pharyngitis Rhinitis
Investigation		Increased blood creatine phosphokinase Increased alanine aminotransferase Increased aspartate aminotransferase Abnormal liver function test Weight increase
Nervous system disorder	Somnolence Headache Dizziness	Disturbance in attention
Respiratory, thoracic and mediastinal disorders		Epistaxis Nasal dryness Upper respiratory disorders Cough Dry throat
Gastrointestinal disorders	Dry mouth	Nausea Upper abdominal pain Diarrhoea Dyspepsia Vomiting Abdominal pain Constipation

Skin and subcutaneous tissue disorders		Rash
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 Irritability

Post-marketing experience

Additional, rare adverse events, spontaneously reported with use of RUPANASE 10 include nasal dryness, genital erythema, erythema, conjunctival hyperaemia, blepharitis and blister, disorientation, abnormal gait, increased sweating, tremor and headache.

Additionally, two rare adverse reactions were reported in the post-authorisation period: Tachycardia and palpitations and hypersensitivity reactions (including anaphylactic reactions, angioedema and urticarial) have been reported in post-marketing experience with RUPANASE 10 tablets.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of RUPANASE 10. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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) have an antihistaminic activity and may contribute to the overall efficacy of 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, 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. After a dose of 10 mg/day for 7 days, the 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

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 ($_{tmax}$) 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.

Distribution

Rupatadine is 98 % to 99 % bound to human plasma proteins.

Metabolism

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.

Cytochrome P450 CYP3A4 was identified in vitro as the main isoenzyme responsible for the biotransformation of rupatadine but other CYP isoenzymes like CYP2C9, CYP2C19 and CYP2D6 are also involved.

Elimination

The plasma concentration exhibited a bi-exponential decay, with a mean elimination half-life of 5,9 hours. In a study of excretion in humans (40 mg of ^{14}C-rupatadine), 34,6 % of the radioactive drug administered was recovered in urine and 60,9 % in faeces collected over 7 days. Biliary excretion is the most important elimination route for rupatadine.

Rupatadine undergoes considerable pre-systemic metabolism when administered by oral route. The amounts of unaltered active substance found in urine and faeces were insignificant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Lactose monohydrate

Magnesium stearate

Pregelatinised maize starch

Red iron oxide (E-172)

Yellow iron oxide (E-172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.

Store at or below 30 °C.

6.5 Nature and contents of container

RUPANASE 10 tablets are packed in the following:

PVC-PVDC foil and aluminium blister packaging.

In pack sizes of 10 (1 strip of 10 tablets), 20 (2 strips of 10 tablets) or 30 (2 strips of 15 tablets) in a cardboard carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

iNova Pharmaceuticals (Pty) Ltd

15e Riley Road

Bedfordview

South Africa

8. REGISTRATION NUMBER

RUPANASE 10: 46/5.7.1/0119

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

02 October 2014

10. DATE OF REVISION OF THE TEXT

10 August 2021