PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

RAPUTEZE™, tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg rupatadine, as rupatadine fumarate.

Contains sugar (lactose monohydrate 38 mg/tablet).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Light-salmon coloured, round tablets, approximately 6,35 mm in diameter.

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.

Special populations

Elderly

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

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to rupatadine or to any of the excipients listed in section 6.1.
- RAPUTEZE is not recommended for use in children below 12 years of age.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Renal and hepatic impairment

As there is no data of patients with impaired kidney or liver functions, the use of RAPUTEZE is not recommended in these patients.

Grapefruit juice

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

CYP3A4 inhibitors

The combination of RAPUTEZE 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).

Cardiac safety

RAPUTEZE should be used with caution in patients with known prolongation of the QT interval, patients with uncorrected hypokalaemia, patients with ongoing pro-dysrhythmia conditions, such as clinically significant bradycardia and acute myocardial ischemia.

Use in the elderly

RAPUTEZE should be used with caution in elderly patients (65 years and older).

Although no overall differences in effectiveness or safety were documented, higher sensitivity of some older individuals cannot be excluded (see section 5.2).

Special precaution necessary relating to excipients

RAPUTEZE contains lactose monohydrate (see section 2 and 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose/galactose malabsorption should not take RAPUTEZE.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on rupatadine

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 of the adverse reactions in comparison with these medicines when administered separately.

Interaction with grapefruit:

The concomitant administration of grapefruit juice with RAPUTEZE increased the systemic exposure of rupatadine by 3,5 times. Grapefruit juice should not be taken along with RAPUTEZE.

Effects of rupatadine on other medicines

Caution should be taken when RAPUTEZE is co-administered with other metabolised medicines with narrow therapeutic windows since knowledge of the effect of rupatadine on other medicines 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 central nervous system (CNS) depressants:

As with other antihistamines, such as RAPUTEZE, interactions with CNS depressants cannot be excluded.

Interaction with statins:

Asymptomatic creatine phosphokinase (CPK) increases have been reported. 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 co-administered with statins.

Interaction with midazolam:

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

RAPUTEZE is contraindicated (see section 4.3).

Breastfeeding:

RAPUTEZE is excreted in animal milk.

Due to potential harmful effects in neonates, the use of RAPUTEZE should be avoided during breastfeeding (see section 4.3).

Fertility:

There are no clinical data on fertility.

4.7 Effects on ability to drive and use machines

RAPUTEZE causes somnolence and dizziness as per section 4.8. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction to RAPUTEZE has been established (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent adverse reactions reported were somnolence, headache and fatigue.

b. Tabulated summary of adverse reactions

MedDRA System Organ Class/ Frequency	**Side effects**
Infections and Infestations	
Less frequent:	Pharyngitis, rhinitis
Immune system disorders	
Less frequent:	Hypersensitivity reactions (including anaphylactic reactions, angioedema and urticaria)
Metabolism and nutrition disorders	
Less frequent:	Increased appetite
Psychiatric disorders	
Less frequent:	Irritability
Nervous system disorders	
Frequent:	Somnolence, headache, dizziness
Less frequent	Disturbance in attention
Frequency unknown	Disorientation, tremor, increased sweating, abnormal gait

Eye disorders	
Frequency unknown	Conjunctival hyperaemia, blepharitis and blisters
Cardiac disorders	
Less frequent	Tachycardia and palpitations
Respiratory, thoracic and mediastinal disorders	
Less frequent	Epistaxis, nasal dryness, upper respiratory disorders (e.g., cough, dry throat, oropharyngeal/ pain).
Gastrointestinal disorders	
Frequent	Dry mouth
Less frequent	Nausea, upper abdominal pain, diarrhoea, dyspepsia, vomiting, abdominal pain, constipation
Skin and subcutaneous tissue disorders	
Less frequent	Rash
Frequency unknown	Genital erythema, erythema
Musculoskeletal, connective tissue and bone disorders	
Less frequent	Back pain, arthralgia, myalgia
General disorders and administrative site conditions	
Frequent	Fatigue, asthenia
Less frequent	Thirst, malaise, pyrexia
Investigations	
Less frequent	Increased blood creatine phosphokinase, increased alanine aminotransferase, increased aspartate aminotransferase, abnormal liver function test

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 the medicine. Health care 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.

4.9 Overdose

The most common adverse reaction observed was somnolence. If accidental ingestion of very high doses occurs symptomatic treatment together with the required supportive measures should be given. Concomitant medicines taken should also be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.7.1 Antihistaminics

Pharmacotherapeutic group: other antihistamines for systemic use.

ATC code: R06A X28

Rupatadine is a non-sedating, long-acting histamine antagonist, with selective peripheral H_1-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 non-immunological stimuli, and inhibition of the

release of cytokines, particularly of the TNFa in human mast cells and monocytes. Rupatadine shows high H_1-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 (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.

Distribution

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

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.

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

Elimination

In a study of excretion in humans (40 mg of ^{14}C-rupatadine), 34,6 % of the radioactive medicine administered was recovered in urine and 60,9 % in faeces collected over 7 days. Biliary excretion is the most important elimination route for rupatadine.

The amounts of unaltered active substance found in urine and faeces were insignificant.

Specific patient groups

Elderly

Although no dosage adjustments are necessary when RAPUTEZE is used in the elderly, caution is advised.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose PH 102 (E460)

Pregelatinised maize starch

Colour iron oxide red (E 172)

Colour iron oxide yellow (E 172)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister in the original container until required for use.

6.5 Nature and contents of container

Thermoformed blisters made of clear PVC (250 µm)/PVDC (40 g/m^2) and aluminium foil (25 µm).

Blisters are packed in a carton in pack sizes of 10, 20 or 30 tablets.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park

0181

South Africa

Tel: +27 (0)12 997 6974

8 REGISTRATION NUMBER

RAPUTEZE: 57/5.7.1/0071

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 November 2024

10 DATE OF REVISION OF THE TEXT

Not applicable.