Clean Amended Professional Information for Medicines for Human Use: RUTARN 10

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

RUTARN 10 TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RUTARN 10 tablets

Each tablet contains rupatadine fumarate equivalent to 10 mg of rupatadine.

Contains sugar (lactose monohydrate).

Each 10 mg tablet contains 38,0 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RUTARN 10 tablets

Light-salmon round tablets.

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 population

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

Paediatric population

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

Method of administration

RUTARN 10 is for oral administration.

4.3 Contraindications

- Hypersensitivity to rupatadine or to any of the excipients listed in section 6.1.
- RUTARN 10 is not recommended for use in children below 12 years of age.
- RUTARN 10 is not recommended for use in pregnancy and lactation.

4.4 Special warnings and precautions for use

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

CYP3A4 inhibitors: 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).

Cardiac safety of rupatadine was assessed in a reported 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 hypokalaemia, patients with ongoing prodysrhythmic conditions, such as clinically significant bradycardia, acute myocardial ischemia.

Use in elderly: RUTARN 10 should be used with caution in elderly patients (65 years and older). Although no overall differences in effectiveness or safety were observed in reported clinical trials, higher sensitivity of some older individuals cannot be excluded due to the low number of elderly patients enrolled (see section 5.2).

Paediatric patients: regarding use in children less than 12 years old see section 4.2.

Renal and hepatic impairment: as there is no clinical experience in patients with impaired kidney or liver functions, the use of RUTARN 10 is not recommended in these patients.

Excipients: lactose monohydrate

RUTARN 10 contains lactose monohydrate:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults and adolescents (over 12 years of age) with RUTARN 10 tablets.

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 the medicines 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 medicines

Caution should be taken when rupatadine 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.
RUTARN 10 should be used with caution when administered with alcohol.

Interaction with CNS depressants

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 co-administered with statins.

4.6 Fertility, pregnancy and lactation

Pregnancy

RUTARN 10 is contraindicated in pregnancy. See section 4.3.

Breastfeeding

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

Fertility

There are no clinical data on fertility. Studies reported 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 ability to drive and use machines

At the recommended dose, RUTARN 10 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

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

The majority of the adverse reactions observed in reported clinical trials were mild to moderate in severity and they usually did not require cessation of therapy.

The table below shows all adverse drug reactions (ADRs) observed during clinical trials.

System Organ Class	**Frequency**	
	Frequent	**Less Frequent**
Infections and infestations		Pharyngitis, rhinitis
Immune system disorders		Hypersensitivity reactions (including anaphylactic reactions, angioedema and urticaria) *
Metabolism and nutrition disorders		Increased appetite

Psychiatric disorders		Irritability
Nervous system disorders	Somnolence, Headache, Dizziness	Disturbance in attention
Cardiac disorders		Tachycardia and palpitations *
Respiratory, thoracic and mediastinal disorders		Epistaxis, nasal dryness, cough, dry throat, oropharyngeal pain, upper respiratory disorders
Gastrointestinal disorders	Dry mouth	Nausea, abdominal pain upper, diarrhoea, dyspepsia, vomiting, abdominal pain, constipation
Skin and subcutaneous tissue disorders		Rash
Musculoskeletal and connective tissue disorders		Back pain, arthralgia, myalgia

General disorders and administration site conditions	Fatigue, Asthenia	Thirst, malaise, pyrexia
Investigations		Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver function test abnormal, weight increased

* tachycardia, palpitations and hypersensitivity reactions (including anaphylactic reactions, angioedema and urticarial) have been reported in post-marketing experience with RUTARN 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 the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za.

4.9 Overdose

If accidental ingestion of very high doses occurs symptomatic treatment together with the required supportive measures should be given, taking into account any concomitantly ingested medications.

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

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 TNFα 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 (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 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 14C-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.

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

Iron oxide red E172

Iron oxide yellow E172

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose [~~P~~]pH 102

Starch, pregelatinised (Maize)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C

6.5 Nature and contents of container

Thermoformed blisters made of Aluminium and PVC/PVdC clear film.

Pack of 10, 20 or 30 tablets in a cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

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52/5.7.1/0184

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12 July 2022

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