PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

RUPASTRAL 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg rupatadine as rupatadine fumarate.

Contains sugar: lactose monohydrate 60 mg/tablet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Light-salmon coloured, round, biconvex, uncoated tablets, plain on both sides.

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

Rupatadine 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 (see section 6.1).
- RUPASTRAL 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 renal or liver functions, the use of RUPASTRAL is not recommended in these patients.

Grapefruit juice

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

Cardiac safety

RUPASTRAL 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 and acute myocardial ischemia.

Use in the elderly

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

Paediatric patients

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

Excipient warning

RUPASTRAL contains lactose monohydrate. Patients with rare hereditary condition of galactose intolerance, e.g. galactosemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take RUPASTRAL.

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 inhibitors

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. (2)

The concomitant administration of RUPASTRAL and ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2 to 3 times respectively.

Alcohol

RUPASTRAL should be used with caution when administered with alcohol. (1)

Grapefruit

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

CNS depressants

Interactions with CNS depressants cannot be excluded.

SSRI antidepressant

No interactions have been observed with fluoxetine.

Statins

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

Midazolam

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

Medicines with narrow therapeutic windows

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

4.6 Fertility, pregnancy and lactation

Pregnancy

RUPASTRAL is contraindicated during pregnancy (see section 4.3).

Breastfeeding

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

At the recommended dosage, RUPASTRAL is not expected to influence the ability to drive or use machinery. Nevertheless, RUPASTRAL may cause somnolence, headache, dizziness and a disturbance in attention; thus, care should be taken before driving or using machinery until the patient's individual reaction to RUPASTRAL 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, fatigue, asthenia, dry mouth and dizziness.

b. Tabulated summary of adverse reactions

MedDRA System Organ Class	**Frequency**	**Side Effects**
Infections and Infestations	Less frequent	Pharyngitis, rhinitis
Immune system disorders	Frequency unknown	Hypersensitivity reactions (including anaphylactic reactions, angioedema and urticarial)
Metabolism and nutrition disorders	Less frequent	Increased appetite
Psychiatric disorders	Less frequent	Irritability

MedDRA System Organ Class	Frequency	Side Effects
Nervous system disorders	Frequent	Somnolence, headache, dizziness
	Less frequent	Disturbance in attention
	Frequency unknown	Disorientation, abnormal gait, increased sweating
Eye disorders	Frequency unknow	Conjunctiva! hyperaemia, blepharitis and blister
Cardiac disorders	Frequency unknown	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

MedDRA System Organ Class	Frequency	Side Effects
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	Increase weight, 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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

The most common adverse reaction when 100 mg rupatadine was taken for 6 days 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 taken into account.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 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 (AUG) 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.

Rupatadine undergoes considerable pre-systemic metabolism when administered by oral route. Cytochrome P450 CYP3A4 was identified *in vitro* as the main isoenzyme responsible for the biotransformation of rupatadine, but other CYP isoenzymes like CYP2C9, CYP2C1 Band CYP2D6 are also involved.

Elimination

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 feces collected over 7 days. Biliary excretion is the most important elimination route for rupatadine. The amounts of unaltered active substance found *in* urine and feces were insignificant.

Linearity

Pharmacokinetics of rupatadine was linear for a dose between 10 and 20 mg after single and repeated doses.

Specific patient groups

Elderly

Data comparing 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 analyses. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Microcrystalline cellulose (E460)

Pregelatinised maize starch

Colour iron oxide red (E172)

Colour iron oxide yellow (E172)

Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep blister in original container to protect from light.

6.5 Nature and contents of container

PVC/PVDC and aluminium blister.

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

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Astral Pharma (Pty) Ltd

125 Meade Street

1st Floor, Beacon Place

George, 6529

8 REGISTRATION NUMBER

57/5.7.1/0199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 May 2025

10 DATE OF REVISION OF THE TEXT

27 May 2025

Date/sign ___  __May2025_FIN