PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

RAZTROL (Tablets 10 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Rupatadine fumarate 12,79 mg equivalent to rupatadine 10 mg.

For full list of excipients, see section 6.1

Contains sugar: lactose monohydrate 60 mg per tablet.

3. PHARMACEUTICAL FORM

Tablet.

RAZTROL is a salmon coloured, 6,35 mm ± 0.1 mm 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.

Method of Administration

For oral use.

4.3 Contraindications

- Hypersensitivity to rupatadine or to any of the excipients of RAZTROL listed in section 6.1.
- RAZTROL tablets are 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 reported in patients with impaired kidney or liver functions, the use of RAZTROL is not recommended in these patients.

Paediatric patients: RAZTROL is not recommended for use in children under 12 years as safety is not reported.

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

Cardiac safety: RAZTROL 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: RAZTROL should be used with caution in elderly patients (65 years and older). Although no overall differences in effectiveness or safety were reported in clinical trials, higher sensitivity of some older individuals cannot be excluded.

CYP3A4 inhibitors: The combination of rupatadine with potent CYP3A4 inhibitors should be avoided and with moderate CYP3A4 inhibitors should be administered with caution. 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).

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

4.5 Interaction with other medicines and other forms of interaction

***Interaction with alcohol*:** RAZTROL should be used with caution when administered with alcohol.

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

***Interaction with CNS depressants*:** Interactions with other CNS depressants has not been reported. No interactions have been reported with fluoxetine.

***Interaction with statins*:** Asymptomatic creatine phosphokinase (CPK) increases have been reported in clinical trials of rupatadine. The risk of interactions with statins, some of which are also metabolised by the cytochrome P450 CYPA4 isoenzyme, is unknown. Rupatadine should be used with caution when co-administered with statins.

CYP3A4 inhibitors: The concomitant administration of RAZTROL and ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2-3 times respectively. 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 (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy: RAZTROL is contraindicated in pregnancy.

Lactation: 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 reported clinical data on fertility. A significant reduction of fertility in animals have been reported at exposure levels higher than those reported in humans at the maximum therapeutic dose.

4.7 Effects on ability to drive and use machines

At the recommended dosage, RAZTROL 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 RAZTROL has been reported.

4.8 Undesirable Effects

SIDE EFFECTS

System Organ Class	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 disorder	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 Upper abdominal pain 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	-	Increased blood creatine phosphokinase Increased alanine aminotransferase Increased aspartate aminotransferase Abnormal liver function test Weight increased Increased weight

* tachycardia and palpitations and hypersensitivity reactions (including anaphylactic reactions, angioedema and urticarial) have been reported in post-marketing experience with rupatadine 10 mg tablets.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **t**he medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the

Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Suspected adverse reactions can also be reported directly to the HCR via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000.

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 H_1-receptors.

At the recommended dose of 10 mg, the reported 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 Tumour Necrosis Factor alpha (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 reported to be 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 reported 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 reported to be 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 reported to be 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 reported to be 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 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

Iron oxide yellow

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Pre-gelatinised starch.

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 30 ºC. Keep the blister in the outer carton in order to protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

RAZTROL tablets are packed in blister packs consisting of PVC/PVDC foil as a forming material and pre-printed aluminium foil as a lidding material. Each blister will contain 10 tablets. Three such blisters will be packed in a pre-printed carton.

6.6 Special precautions for disposal and other handling

No special requirement for disposal

7. HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

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8. REGISTRATION NUMBERS

55/5.7.1/0293

9. DATE OF FIRST AUTHORISATION

7 December 2021

10. DATE OF REVISION OF THE TEXT

30 October 2026