PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF MEDICINE
RUALIDINE 10, 10 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 12,79 mg rupatadine fumarate, equivalent to 10 mg rupatadine.
Excipient with known effect:
Contains sugar: lactose monohydrate 60,00 mg per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablets.
Salmon coloured, 6,35 mm ± 0,1 mm round, biconvex, uncoated tablets, plain on both sides.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
RUALIDINE 10 is indicated for the 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
Use in the elderly:
RUALIDINE 10 should be used with caution in elderly people (see section 4.4).

Use in renal or hepatic dysfunction:
As there is no clinical experience in patients with impaired kidney or liver functions, the use of RUALIDINE 10 is not recommended in these patients (see section 4.4).

Paediatric population
RUALIDINE 10 is not recommended for use in children under 12 years as safety has not been established (see section 4.4).

Method of administration
For oral administration with or without food.
RUALIDINE 10 should not be administered with grapefruit juice (see section 4.5).

4.3 Contraindications
- Hypersensitivity to rupatadine or to any of the excipients listed in section 6.1;
- Children below 12 years of age (see section 4.4);
- Pregnancy and lactation (see section 4.6).

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 RUALIDINE 10 is not recommended in these patients.

Cardiac safety
Cardiac safety of rupatadine was assessed in a 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, RUALIDINE 10 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.

Elderly population
RUALIDINE 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 due to the low number of elderly patients enrolled (see section 5.2).

Lactose
RUALIDINE 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
Effects of other medicines on RUALIDINE 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 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.

Effects of grapefruit juice on RUALIDINE 10
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 RUALIDINE 10.

Effects of RUALIDINE 10 on other medicines
Caution should be taken when RUALIDINE 10 is co-administered with other metabolised medicines with narrow therapeutic windows since knowledge of the effect of rupatadine on other medicines are limited.

Interaction with CNS depressants:
Interactions with CNS depressants cannot be excluded. No interactions have been observed with fluoxetine.

Interaction with 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.

Interaction with statins:
Asymptomatic Creatine Phosphokinase (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, RUALIDINE 10 should be used with caution when it is co-administered with statins.

Effects of alcohol on RUALIDINE 10:
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.
RUALIDINE 10 should be used with caution when administered with alcohol.

4.6 Fertility, pregnancy and lactation
Pregnancy
RUALIDINE 10 is contraindicated in pregnancy.

Breastfeeding
RUALIDINE 10 is contraindicated in lactation. Rupatadine is excreted in animal milk. Due to potential harmful effects in neonates, the use of RUALIDINE 10 should be avoided during breastfeeding.

Fertility
There are no clinical data on fertility.

4.7 Effects on ability to drive and use machines
At the recommended dosage, RUALIDINE 10 is not expected to influence the ability to drive or use machinery. However, dizziness and attention disturbances has been reported (see section 4.8). Care should be taken before driving or using machinery until the patient's individual reaction on RUALIDINE 10 has been established.

4.8 Undesirable effects
a. Summary of the safety profile
The most frequent adverse reactions in controlled clinical studies were somnolence, headache, fatigue, asthenia, dry mouth and dizziness.

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Less frequent*	Pharyngitis, rhinitis.
Metabolism and nutrition disorders	*Less frequent*	Increase appetite.
Psychiatric disorders	*Less frequent*	Irritability.
Nervous system disorders	*Frequent*	Dizziness, headache, somnolence.
	Less frequent	Disturbance in attention.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Cough, dry throat, epistaxis, nasal dryness, oropharyngeal pain, Upper respiratory disorders.
Gastrointestinal disorders	*Frequent*	Dry mouth.
	Less frequent	Abdominal pain, abdominal pain upper, diarrhoea, dyspepsia, nausea, vomiting, constipation.
Skin and subcutaneous tissue disorders	*Less frequent*	Rash.
Musculoskeletal and connective tissue disorders	*Less frequent*	Arthralgia, back pain, myalgia.
General disorders and administration site conditions	*Frequent*	Asthenia, fatigue.
	Less frequent	Malaise, pyrexia, thirst.
Investigations	*Less frequent*	Alanine aminotransferase increased, aspartate aminotransferase increased, blood creatine phosphokinase increased, liver function test abnormal, weight increase.

Post-marketing experience:
Additional adverse events, spontaneously reported with use of rupatadine include nasal dryness, hypersensitivity reactions (including anaphylactic reactions, angioedema, urticarial, genital erythema, erythema, conjunctival hyperaemia, blepharitis, and blister), disorientation, abnormal gait, Increased sweating, tremor, headache, tachycardia, and palpitations.

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 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.

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
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 second-generation, 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) retain an antihistaminic activity and may partially contribute to the overall efficacy of rupatadine and a long duration of action.
Rupatadine possesses antihistamine properties such as the inhibition or the degranulation or mast cells induced by immunological and nonimmunological stimuli, and inhibition of the release of cytokines, particularly of the TNF_a in human mast cells and monocytes.
Rupatadine shows high H_1-receptor affinity and little or no activity on other CNS receptors.

Paediatric population
No data are available in the paediatric population.
RUALIDINE 10 is not recommended for use in children under 12 years as safety has not been established.

5.2 Pharmacokinetic properties
Absorption
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. The plasma concentration followed a bi-exponential drop-off with a mean elimination half-life of 5,9 hours.

Effect of the intake of food:
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
The binding-rate of rupatadine to plasma proteins was 98,5 to 99 %.

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 retained 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 human (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 emanation 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. This means that rupatadine is almost completely metabolised. Roughly, the active metabolites desloratadine and other hydroxylated derivatives accounted for 27 % and 48 %, respectively, of the total systemic exposure of the active substances

Elderly
In a study on healthy volunteers to compare 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 analysed. 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
Iron oxide red (77491)
Iron oxide yellow (77492)
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Pregelatinized starch

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at or below 30 °C.
This medicine does not require any special storage conditions.

6.5 Nature and contents of container
RUALIDINE 10 is packed in blister packs consisting of white colour PVC/PVDC foil as the forming material and pre-printed aluminium foil as the lidding material. Each blister contains 10 tablets. The blisters are packed in cartons.
Pack sizes: 10, 20, 30 tablets.
Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling
No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDERS OF CERTIFICATE OF REGISTRATION
Strides Pharma (SA) (Pty) Ltd.
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8 REGISTRATION NUMBER
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