

## SCHEDULING STATUS

S2

### 1. NAME OF THE MEDICINE

RUPALLERG 10, Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is rupatadine fumarate 12,80 mg equivalent to rupatadine 10 mg base.

Contains sugar. Each tablet contains lactose monohydrate 61,100 mg per tablet.

For the full list of excipients, see section 6.1

### 3. PHARMACEUTICAL FORM

Tablets

RUPALLERG 10 tablets are round, biconvex, light salmon pink in colour with no markings.

### 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.

##### Special populations

##### *Elderly:*

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

##### Paediatric population

RUPALLERG 10 is not recommended for use in children below 12 years of age (see section 4.3).

#### **Method of administration**

Oral use.

RUPALLERG 10 can be taken with or without food.

#### **4.3 Contraindications**

Hypersensitivity to the active substance, rupatadine, or to any of the excipients as listed in section 6.1.

RUPALLERG 10 is 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 in patients with impaired kidney or liver functions, the use of RUPALLERG 10 is not recommended in these patients.

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

The combination of RUPALLERG 10 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 RUPALLERG 10 may increase plasma concentrations of these drugs (see section 4.5).

##### *Cardiac Safety*

RUPALLERG 10 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*

RUPALLERG 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.

#### *Excipients with known effect*

Due to the presence of lactose monohydrate, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take RUPALLERG 10.

#### **Paediatric population**

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

#### **4.5 Interactions with other medicines and other forms of interactions.**

##### **Effects of other medicine on RUPALLERG 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 RUPALLERG 10 and ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2-3 times respectively.

Interaction with grapefruit: The concomitant administration of grapefruit juice with RUPALLERG 10 increased the systemic exposure of rupatadine by 3,5 times. It is recommended to avoid intake of grapefruit juice along with RUPALLERG 10.

## **Effects of RUPALLERG 10 on other medicine**

Caution should be taken when RUPALLERG 10 is co-administered with other metabolised medicine with narrow therapeutic windows since knowledge of the effect of RUPALLERG 10 on other medicine is limited.

*Interaction with alcohol:* RUPALLERG 10 should be used with caution when administered with alcohol. After administration of alcohol, a dose of RUPALLERG 10 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 CNS depressants:* Interactions with other CNS depressants has not been established. No interactions have been observed with fluoxetine.

*Interaction with statins:* Asymptomatic CPK increases have been reported in RUPALLERG 10 clinical trials. The risk of interactions with statins, some of which are also metabolized by the cytochrome P450 CYP3A4 isoenzyme, is unknown. RUPALLERG 10 should be used with caution when co-administered with statins.

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

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

RUPALLERG 10 is contraindicated.

### **Breastfeeding**

RUPALLERG 10 is excreted in animal milk. Due to potential harmful effects in neonates, the use of RUPALLERG 10 should be avoided during breastfeeding.

## **4.7 Effects on ability to drive and use machines**

At the recommended dosage, RUPALLERG 10 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 RUPALLERG 10 has been established.

#### 4.8 Undesirable effects

<b>System Organ Class</b>	<b>Common (<math>\geq 1/100</math> to <math>&lt; 1/10</math>)</b>	<b>Uncommon (<math>\geq 1/1000</math> to <math>&lt; 1/100</math>)</b>
Infections and infestations		Pharyngitis Rhinitis
Investigation		Increased blood creatine phosphokinase Increased alanine aminotransferase Increased aspartate aminotransferase Abnormal liver function test Weight increase
Nervous system disorder	Somnolence Headache Dizziness	Disturbance in attention
Respiratory, thoracic and mediastinal disorders		Epistaxis Nasal dryness Upper respiratory disorders Cough Dry throat
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
Metabolism and nutrition disorders		Increased appetite
General disorders and administration site conditions	Fatigue, Asthenia	Thirst Malaise Pyrexia Irritability

### Post-marketing experience

Additional, rare adverse events, spontaneously reported with use of RUPALLERG 10 include nasal dryness, genital erythema, erythema, conjunctival hyperaemia, blepharitis and blister, disorientation, abnormal gait, increased sweating, tremor and headache.

Additionally, two rare adverse reactions were reported in the post-authorisation period: Tachycardia and palpitations and hypersensitivity reactions (including anaphylactic reactions, angioedema and urticarial) have been reported in post-marketing experience with RUPALLERG 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 RUPALLERG 10. Healthcare 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

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<sub>1</sub>-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 TNF $\alpha$  in human mast cells and monocytes.

Rupatadine shows high H<sub>1</sub> 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.

## **Metabolism**

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 <sup>14</sup>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 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**

Microcrystalline cellulose

Lactose monohydrate

Magnesium stearate

Pregelatinised maize starch

Red iron oxide (E-172)

Yellow iron oxide (E-172)



## **6.2 Incompatibilities**

Not applicable

## **6.3 Shelf life**

3 years

## **6.4 Special precautions for storage**

Keep the blister in the outer carton in order to protect from light.

Store at or below 30 °C.

## **6.5 Nature and contents of container**

RUPALLERG 10 tablets are packed in the following:

PVC-PVDC foil and aluminium blister packaging.

In pack sizes of 10 (1 strip of 10 tablets), or 30 (2 strips of 15 tablets) in a cardboard carton.

## **7. HOLDER OF CERTIFICATE OF REGISTRATION**

iNova Pharmaceuticals (Pty) Ltd

15e Riley Road

Bedfordview

South Africa

## **8. REGISTRATION NUMBER**

RUPALLERG 10: 51/5.7.1/0694

## **9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION**

02 October 2014

## **10. DATE OF REVISION OF THE TEXT**

10 August 2021