1.5.5 CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

[PRODUCT NAME] 1 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of oral solution contains:

1 mg of rupatadine (as fumarate)

Preservative: Methyl parahydroxybenzoate 0,1 % w/v

CONTAINS SUGAR: Sucrose 300 mg/ml

CONTAINS SWEETENER: Saccharin sodium 0,5 mg/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear yellow solution with the smell and flavour of bananas.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

[PRODUCT NAME] is indicated for the symptomatic treatment of:

- Allergic rhinitis (including persistent allergic rhinitis) in children aged 2 to 11 years weighing 10 kg or more.
- Urticaria in children aged 2 to 11 years weighing 10 kg or more.

4.2 Posology and method of administration

Children aged 2 to 11 years:

Children weighing equal to or more than 25 kg:

5 ml (5 mg) once a day, with or without food.

Children weighing equal to or more than 10 kg up to less than 25 kg:

2,5 ml (2.5 mg) once a day, with or without food.

Not recommended for children under 2 years of age.

The administration of [PRODUCT NAME] to children under 2 years of age is not recommended due to the lack of data in this population (see section 4.4).

In adults and adolescents (over 12 years of age), the administration of rupatadine 10 mg tablets is more appropriate.

Patients with renal or hepatic insufficiency: As there is no clinical experience in patients with impaired kidney or liver functions, the use of rupatadine is at present not recommended in these patients.

Instructions for use:

- To open the bottle, press the cap and turn it anticlockwise.
- Take the syringe and put it in the perforated stopper and turn the bottle upside down.
- Fill the syringe with the prescribed dose.
- Administer directly from the dosing syringe.

  Wash the syringe after use.

4.3 Contraindications

Hypersensitivity to rupatadine or to any of the excipients.

[PRODUCT NAME] is not recommended for use in children below 2 years of age.

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Safety of [PRODUCT NAME] in children below 2 years of age has not been established.

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).

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

Cardiac safety of rupatadine 10 mg tablets was assessed in a thorough QT/QTc study in adults. Rupatadine up to 10 times therapeutic dose did not produce any effect on the ECG and hence raises no cardiac safety concerns. However, [PRODUCT NAME] should be used with caution in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia and acute myocardial ischemia.

Increases of blood creatine phosphokinase, alanine aminotransferase and aspartate aminotransferase, as well as abnormalities of liver function tests are uncommon adverse reaction reported with rupatadine 10 mg tablets in adults.

Excipients that may have an effect

[PRODUCT NAME] contains sucrose, so it may be harmful to teeth. Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

[PRODUCT NAME] contains methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Contains sucrose which may have an effect on the glycaemic control of patients with *diabetes mellitus*.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed in children.

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

Effects of other medicines on [PRODUCT NAME]

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 10 mg tablet. This occurs because grapefruit has one or more compounds that inhibit the CYP3A4 and can increase the plasmatic concentrations of medicines metabolised through this CYP3A4, like rupatadine. In addition, it has been suggested that the grapefruit can affect intestinal medicine transport systems as the glycoprotein-P. Grapefruit juice should not be taken simultaneously.

Effects of [PRODUCT NAME] on other medicines

Caution should be taken when [PRODUCT NAME] is co-administered with other metabolised drugs 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 rupatadine 10 mg tablet 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:

As with other antihistamines, interactions with CNS depressants cannot be excluded.

Interaction with statins:

Asymptomatic CPK increases have been reported in rupatadine clinical trials. The risk of interaction with statins, some of which are also metabolised by cytochrome P450 CYP3A4 isoenzyme, is unknown. Rupatadine should therefore be used with caution when co-administered with statins.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a limited number (2) of exposed pregnancies indicate no adverse effects of rupatadine on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of rupatadine during pregnancy (see section 4.3).

Breastfeeding

Rupatadine is excreted in animal milk. It is unknown whether rupatadine is excreted into breast milk. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from rupatadine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman (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 (see section 5.3).

4.7 Effects on ability to drive and use machines

Rupatadine 10 mg had no influence on the ability to drive and use machines in a performed clinical trial. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction to rupatadine has been established.

4.8 Undesirable effects

Infections and infestations

Uncommon (≥ 1/1 000 to < 1/100): Influenza, nasopharyngitis, upper respiratory tract infection

Blood and lymphatic system disorders

Uncommon (≥ 1/1 000 to < 1/100): Eosinophilia, neutropenia

Nervous system disorders

Common (≥ 1/100 to < 1/10): Headache, somnolence

Uncommon (≥ 1/1 000 to < 1/100): Dizziness

Gastrointestinal disorders

Uncommon (≥ 1/1 000 to < 1/100): Nausea

Skin and subcutaneous tissue disorders

Uncommon (≥ 1/1 000 to < 1/100): Eczema, night sweats

General disorders and administration site conditions

Uncommon (≥ 1/1 000 to < 1/100): Fatigue

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 Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8 . Alternately contact iNova Pharmaceuticals (Pty) Ltd. at +27 11 087 0000. Website: www.inovapharma.co.za .

4.9 Overdose

No case of overdose has been reported in adults and children. In a clinical safety study in adults rupatadine at daily dose of 100 mg for 6 days was well tolerated. The most common adverse reaction was somnolence. If accidental ingestion of very high doses occurs symptomatic treatment together with the required supportive measures should be given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological class: A 5.7.1 Antihistaminics.

Rupatadine is a second-generation antihistamine, long-acting histamine antagonist, with selective peripheral H1-receptor antagonist activity. Some of the metabolites (desloratadine and its hydroxylated metabolites) retain an antihistaminic activity and may partially contribute to the overall efficacy of the medicine.

In vitro studies with rupatadine at high concentration have shown an inhibition of the degranulation of mast cells induced by immunological and non-immunological stimuli as well as the release of cytokines, particularly of the TNFα in human mast cells and monocytes.

5.2 Pharmacokinetic properties

Paediatric population

In the subgroup of children 2 – 5 and 6 – 11 years old, rupatadine was rapidly absorbed with a mean Cmax of 1,9 and 2,5 ng/ml after repeated oral dose, respectively. In terms of exposition, the mean total area under the curve (AUC) value was 10,4 ng.h/ml in children 2 – 5 years and 10,7 ng.h/ml in children 6 – 11 years. All these values are similar to those obtained in adults and adolescents.

The mean elimination half-life of rupatadine in children 2 -5 years was 15,9 hours and in children 6 - 11 years was 12,3 hours, which are longer than that reported with tablets in adults and adolescents.

Effect of the intake of food

No interaction food study has been performed with rupatadine oral solution. The influence of food was performed in adults and adolescents with rupatadine 10 mg tablets. Intake of food increased the systemic exposure (AUC) to rupatadine by about 23 %. The maximum plasma concentration (Cmax) was not affected by food intake. These differences had no clinical significance.

Metabolism and elimination

In a study of excretion in adults, 34,6 % of rupatadine administered was recovered in urine and 60,9 % in faeces collected over 7 days. 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. In vitro metabolism studies in human liver microsomes indicate that rupatadine is mainly metabolised by the cytochrome P450 (CYP 3A4).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

More than 100 times the clinically recommended dose in adults (10 mg) of rupatadine did neither extend the QTc or QRS interval nor produce arrhythmia in various species of animals such as rats, guinea pigs and dogs. Rupatadine and one of its main active metabolites in humans, 3-hydroxydesloratadine, did not affect the cardiac action potential in isolated dog Purkinje fibres at concentrations at least 2000 times greater than the Cmax reached after the administration of a dose of 10 mg in humans. In a study that evaluated the effect on cloned human HERG channel, rupatadine inhibited that channel at a concentration 1685 times greater than the Cmax obtained after the administration of 10 mg of rupatadine. Studies of tissue distribution in rats with radiolabelled rupatadine showed that rupatadine does not accumulate in heart tissue.

In the rat, a significant reduction of male and female fertility occurred at the high dose of 120 mg/kg/day, providing Cmax 268 times those measured in humans at the therapeutic dose (10 mg/day). Foetal toxicity (growth delay, incomplete ossification, minor skeletal findings) was reported in rats at maternotoxic dose-levels only (25 and 120 mg/kg/day). In rabbits, no

evidence of developmental toxicity was noted at doses up to 100 mg/kg. The developmental No Adverse Effect Levels were determined at 5 mg/kg/day in rats and 100 mg/kg/day in rabbits, yielding Cmax 45 and 116 times higher, respectively, than those measured in humans at the therapeutic dose (10 mg/day).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol

Citric acid anhydrous

Disodium phosphate anhydrous

Saccharin sodium

Sucrose

Methylparahydroxybenzoate (E218)

Quinoline yellow (E104) (pure dye, monosulfonated colour, disulfonated colour, trisulfonated colour)

Banana flavour (a blend of natural identical flavouring substances, flavouring preparations and propylene glycol)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

The shelf life after first opening is the same as the expiry date placed on the box and the bottle.

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the bottle in the carton until required for use.

Keep bottle well closed.

Do not refrigerate. Shake the bottle before use.

6.5 Nature and contents of container

120 ml amber polyethylene terephthalate (PET) bottle with a low density polyethylene (LDPE) perforated stopper closed with a yellow high density polyethylene (HDPE) child-resistant cap. The bottle is packed in a cardboard box also containing a 5 ml two-piece oral syringe, consisting of a transparent polypropylene barrel and a transparent HDPE plunger, graduated at 0,25 ml.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

Rupanase Junior: 50/5.7.1/0569

Rupallerg Junior: 50/5.7.1/0570

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 June 2020