FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Rupafin oral solution 1 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains:
1 mg of rupatadine (as fumarate)

Excipients with known effect
Sucrose 300 mg/ml
Methyl Parahydroxybenzoate 1.00 mg/ml
Propylene glycol 200 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, yellow solution with smell and flavor of bananas.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rupafin oral solution 1 mg/ml is indicated for the symptomatic treatment of:
-Allergic rhinitis (including persistent allergic rhinitis) in children aged 2 to 11 years (see section 5.1).
-Urticaria in children aged 2 to 11 years (see section 5.1).

4.2 Posology and method of administration

- Children aged 2 to 11 years

Dosage in children weighing equal or more than 25 kg: 5 ml (5 mg of rupatadine) of oral solution once a day, with or without food.

Dosage in children weighing equal or more than 10 kg up to less than 25 kg: 2.5 ml (2.5 mg of rupatadine) of oral solution once a day, with or without food.

- Children aged under 2 years

The administration of the product to children aged under 2 years is not indicated due to the lack of data in this population (see section 4.4).

- Adults and adolescents (over 12 years of age)

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.

Method of administration

For oral use.

Instructions of 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 the active substance or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Safety of rupatadine oral solution in children aged less than 2 years 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. cyclosporin, tacrolimus, sirolimus, everolimus, cisapride) could be required as rupatadine may increase plasma concentrations of these drugs (see section 4.5).

The administration of rupatadine 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, rupatadine 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, 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.

This medicinal product contains sucrose, so it may be harmful to the teeth. Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicinal product contains methyl parahydroxybenzoate, may cause allergic reactions (possibly delayed).

This medicine contains 200 mg propylene glycol in each ml.

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

This medicine contains less than 1 mmol sodium (23 mg) per 1 ml, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed in children with rupatadine oral solution.

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

Effects of other drugs on rupatadine

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 drugs 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 drugs metabolised through this CYP3A4, like rupatadine. In addition, it has been suggested that the grapefruit can affect intestinal drug transport systems as the glycoprotein-P. Grapefruit juice should not be taken simultaneously.

Effects of rupatadine on other drugs

Caution should be taken when rupatadine is co-administered with other metabolised drugs with narrow therapeutic windows since knowledge of the effect of rupatadine on other drugs 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 uncommonly reported in rupatadine clinical trials. The risk of interactions with statins, some of which are also metabolised by the cytochrome P450 CYP3A4 isozyme, is unknown. For these reasons, rupatadine should be used with caution when it is co-administered with statins.

Interaction with midazolam: After the administration of 10 mg rupatadine in combination with 7.5 mg midazolam, an increase of exposure (Cmax and AUC) of midazolam was mildly higher observed. For this reason, rupatadine acts as a mild inhibitor of CYP3A4.

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/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of rupatadine during pregnancy.

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.

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 the ability to drive and use machines

Rupatadine 10 mg tablets 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

Clinical trials with rupatadine oral solution in children aged 2-11 years included 626 patients. From these, 147 patients were treated with rupatadine 2.5 mg, 159 patients were treated with rupatadine 5 mg, 249 received placebo and 71 received desloratadine.

The frequencies of adverse reactions are assigned as follows:

- *Common (≥ 1/100 to < 1/10)*
- *Uncommon (≥ 1/1,000 to < 1/100)*

The frequencies of adverse reactions reported in patients treated with rupatadine oral solution during clinical trials were as follows:

System Organ Class term		Rupatadine 2.5 mg	Rupatadine 5 mg	Placebo
Frequency	*Preferred term*	(n=147)	(n=159)	(n=249)
	Infections and infestations			
Uncommon	*Influenza*	0	1 (0.63%)	0
	Nasopharyngitis	1 (0.68%)	0	0
	Upper respiratory tract infection	1 (0.68%)	0	0
	Blood and lymphatic system disorders			
Uncommon	*Eosinophilia*	0	1 (0.63%)	0
	Neutropenia	0	1 (0.63%)	0
	Nervous system disorders			
Common	*Headache*	2 (1.36%)	4 (2.52%)	4 (1.61%)
	Somnolence	0	2 (1.26%)	0
Uncommon	*Dizziness*	0	1 (0.63%)	1 (0.40%)
	Gastrointestinal disorders			
Uncommon	*Nausea*	0	1 (0.63%)	2 (0.80%)
	Skin and subcutaneous tissue disorders			
Uncommon	*Eczema*	0	1 (0.63%)	1 (0.40%)
	Night sweats	0	1 (0.63%)	0
	General disorders and administration site conditions			
Uncommon	*Fatigue*	0	1 (0.63%)	0

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
Additionally, you should also report to Kamada Ltd. to email address: pharmacovigilance@kamada.com

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 during 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

Pharmacotherapeutic group: other antihistamines for systemic use, ATC code: R06A X28.

Rupatadine is a second-generation antihistamine, long-acting histamine antagonist, with selective peripheral H_1-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 drug.

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 TNF_α in human mast cells and monocytes. The clinical relevance of the observed experimental data remains to be confirmed.

Rupatadine oral solution had a similar pharmacokinetic profile in children between 6-11 years to that in adults (>12 years): a pharmacodynamic effect was also observed (suppression of the wheal area, antihistamine effect) after 4 weeks of treatment. A randomised, double-blind and placebo-controlled confirmatory study in children with persistent allergic rhinitis aged 6 to 11 years, showed that rupatadine oral solution had a better profile in the reduction of nasal symptoms (rhinorrea and itchy nose mouth throat and/or ears) than placebo in children with persistent allergic rhinitis after 4 and 6 weeks of treatment. Furthermore, a significant improvement in quality of life was also observed throughout the study in comparison with placebo.

Chronic spontaneous urticaria was studied as a clinical model to assess the efficacy of antiH_1 compounds for all urticarial conditions, since the underlying pathophysiology is similar, regardless of etiology, and basically these chronic patients can be more easily recruited into a clinical study. Urticaria is a mast cell-driven disease and histamine and other mediators (PAF and cytokines) are the principal mediators to develop all urticarial lesions. Since rupatadine has capacity to block the release of histamine and other inflammatory mediators, it is expected to be effective treatment in providing symptomatic relief for other urticarial conditions, in addition to chronic spontaneous urticaria, as recommended in clinical guidelines.

The efficacy of rupatadine oral solution in chronic spontaneous urticaria in children aged 2-11 years has been demonstrated in a multicentre, randomized, active- and placebo-controlled study. Overall, 206 children were included. Of them, 113 were between 2-5 years and 93 of them were between 6-11 years. Children were treated with rupatadine (n=66), placebo (n=69) or desloratadine (n=71). Rupatadine dose administered was 2.5 mg in children weighting up to 25 kg and 5 mg in children weighting over 25 kg. Desloratadine dose administered was 1.25 mg in children weighting up to 25 kg and 2.5 mg in children weighting over 25 kg. A statistically significant improvement versus placebo was demonstrated in the mean change in weekly urticaria activity score (UAS7; comprising hives and pruritus), the main endpoint, evaluated after 6 weeks of treatment (rupatadine -11.77 vs. placebo -5.55; $p < 0.001$).The mean percent reduction in the weekly number of hives at study endpoint versus baseline was 56.7% with rupatadine, 49.4% with desloratadine and 22.7% with placebo. The mean percent reduction in pruritus at study endpoint versus baseline was 56.8% with rupatadine, 46.7% with desloratadine and 33.4% with placebo. Both active treatments (rupatadine and desloratadine) achieved statistically significant greater improvements than placebo in the reduction in hives and pruritus, while there were not statistically significant differences between the active treatments regarding these outcomes. The percentage of patient responders of more than 50% in weekly urticaria activity score (UAS7 scale; urticaria and pruritus) was observed in 61% of children treated with rupatadine compared with 36% of children treated with placebo and 54% of children treated with desloratadine.

Clinical trials in volunteers (n= 393) and patients (n=2,650) with allergic rhinitis and chronic

idiopathic urticaria did not show significant effect on the electrocardiogram when rupatadine tablets was administered at doses ranging from 2 mg to 100 mg.

5.2 Pharmacokinetic properties

Paediatric population

In the subgroup of children 2-5 and 6-11 years old, rupatadine was rapidly absorbed and the mean C_{max} was of 1.9 and 2.5 ng/ml after repeated oral dose, respectively. In term 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 h and in children 6-11 years was 12.3 h, 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 (C_{max}) 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).

Based on in vitro studies the inhibitory potential of rupatadine towards CYP1A2, CYP2B6, CYP2C8, CYP2C19, UGT1A1 and UGT2B7, is unlikely. Rupatadine is not expected to inhibit the following transporters in the systemic circulation OATP1B1, OATP1B3 and BCRP (breast cancer resistance protein) hepatic and intestinal. Furthermore, a mild inhibition was detected of the intestinal P-gp (P-glycoprotein).

An in vitro induction CYP study the risk of CYP1A2, CYP2B6 and CYP3A4 induction in the liver in vivo by rupatadine is considered unlikely. Based on in vivo study, rupatadine acts as a mild inhibitor of CYP3A4.

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 2,000 times greater than the C_{max} 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 1,685 times greater than the C_{max} 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 C_{max} 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 C_{max} 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

Sucrose
Propylene glycol
Disodium phosphate anhydrous
Citric acid anhydrous
Banana flavour
Methyl parahydroxybenzoate
Saccharin sodium
Quinoline yellow (E104)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
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 room temperature, below 25°C.

6.5 Nature and contents of the container

125 ml amber polyethylene terephthalate (PET) bottle with low density polyethylene (LDPE) perforated stopper closed with yellow high density polyethylene (HDPE) child-resistant closure in a cardboard box also containing 5 ml oral syringe (polypropylene, polyethylene) 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. Manufacturer

Noucor Health S.A., Barcelona, Spain

8. License holder

Kamada Ltd., Beit Kama, Israel

9. License number

166-17-35846

Revised in November 2022 according to the MOHs guidelines