

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrRUPALL™

Rupatadine Tablets

Tablet, 10 mg rupatadine (as rupatadine fumarate), Oral

Rupatadine Oral Solution

Solution, 1 mg/mL rupatadine (as rupatadine fumarate), Oral

Histamine H₁-Receptor Antagonist
Platelet Activating Factor Receptor Antagonist

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Date of Preparation:
JAN 26, 2023

Submission Control No.: 270596

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet / 10 mg Oral Solution / 1 mg/mL	Tablets: lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch, red iron oxide and yellow iron oxide Oral Solution: banana flavor, citric acid anhydrous, disodium phosphate anhydrous methyl parahydroxybenzoate, propylene glycol, purified water, quinoline yellow, saccharin sodium and sucrose

INDICATIONS AND CLINICAL USE

- **Allergic Rhinitis:** RUPALL (rupatadine) is indicated for the symptomatic relief of nasal and non-nasal symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) in patients 2 years of age and older.
- **Chronic Spontaneous Urticaria:** RUPALL (rupatadine) is indicated for the relief of the symptoms associated with chronic spontaneous urticaria (CSU), e.g. pruritus and hives, in patients 2 years of age and older.

Geriatrics (> 65 years of age):

There is limited information on the use of RUPALL in subjects over 65 years of age. Although no overall differences in effectiveness or safety were observed in clinical trials, higher sensitivity of some older individuals cannot be excluded.

Pediatrics (2-11 years of age):

RUPALL 10 mg tablets are not recommended for use in children below 12 years of age. In these children, oral solution (1 mg/mL) should be used (see DOSING AND ADMINISTRATION).

Pediatrics (<2 years of age):

RUPALL has not been studied in children <2 years of age. RUPALL should not be administered in children <2 years of age.

CONTRAINDICATIONS

RUPALL (rupatadine) is contraindicated in patients with:

- hypersensitivity to rupatadine or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING.
- history of QT prolongation and/or torsade de pointes, including congenital long QT syndromes, history of cardiac arrhythmias (see WARNINGS AND PRECAUTIONS).
- use of CYP3A4 inhibitors or use of other QTc-prolonging drugs (see DRUG INTERACTIONS).

RUPALL Tablets: Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, glucose-galactose malabsorption or the Lapp lactase deficiency should not take RUPALL Tablets.

RUPALL Oral Solution: Due to the presence of sucrose, patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take RUPALL Oral Solution.

WARNINGS AND PRECAUTIONS

General

Co-administration of RUPALL (rupatadine) with ketoconazole and other potent CYP3A4 inhibitors is not recommended (see CONTRAINDICATIONS).

Co-administration of RUPALL with erythromycin and other moderate CYP3A4 inhibitors (azithromycin, fluconazole, diltiazem) should be avoided.

Caution should be taken when RUPALL is co-administered with drugs with narrow therapeutic windows since knowledge of the effect of RUPALL on other drugs is limited.

RUPALL had no influence on the ability to drive and use machines. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction on rupatadine has been established.

Cardiovascular

Rupatadine has been associated with QTc interval prolongation (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). One event of torsade de pointes has been reported with Rupatadine during post-market use (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

RUPALL (rupatadine) should not be used in patients with a history of QTc prolongation and/or torsade de pointes, including congenital long QT syndromes, or a history of other cardiac arrhythmias (see CONTRAINDICATIONS). Concomitant administration of RUPALL with

other QTc prolonging drugs or drugs that inhibit CYP3A4 is contraindicated (see CONTRAINDICATIONS).

Particular care should be exercised when administering RUPALL to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug or drugs that can cause electrolyte imbalance.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Hepatic/Biliary/Pancreatic

There is no clinical experience in patients with hepatic insufficiency. Therefore, the use of RUPALL is not recommended in patients with impaired liver functions.

Immune

Although rare, hypersensitivity reactions (including anaphylactic reactions, angioedema and urticaria) have been reported in post-marketing experience with RUPALL 10 mg tablets.

RUPALL Oral Solution contains methyl parahydroxybenzoate as a preservative, RUPALL Oral Solution may cause allergic reactions (possibly delayed).

Skeletal Muscle Effects

Effects on skeletal muscle such as myalgia, and muscle weakness have been reported in patients treated with rupatadine. Use caution when co-administer with statins.

Renal

There is no clinical experience in patients with renal insufficiency. Therefore, the use of RUPALL is not recommended in patients with impaired kidney functions.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies in pregnant women. Until such data become available, RUPALL should be avoided during pregnancy, unless advised otherwise by a physician.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see TOXICOLOGY). As a precautionary measure due to limited availability of data obtained in pregnant women, it is preferable to avoid the use of RUPALL during pregnancy.

Nursing Women:

Studies in animals indicate that rupatadine is excreted in milk. The extent of excretion in human milk is unknown. Use of RUPALL in nursing mothers is not recommended, unless directed otherwise by a physician.

Pediatrics (2–11 years of age):

RUPALL 10 mg tablets are not recommended for use in children below 12 years of age. In these children oral solution (1 mg/mL) should be used (see DOSING AND ADMINISTRATION).

Pediatrics (<2 years of age):

RUPALL should not be administered to children below 2 years of age due to limited data in this population.

Geriatrics (> 65 years of age):

RUPALL 10 mg tablets 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.

Monitoring and Laboratory Tests:

Increases of blood creatine phosphokinase, alanine aminotransferase and aspartate aminotransferase, as well as abnormalities of liver function tests were uncommonly reported in clinical trials with RUPALL 10 mg tablets in adults (see ADVERSE DRUG REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

ADVERSE REACTIONS**Adverse Drug Reaction Overview*****Adults and Adolescents (12 years and older):***

A total of 3823 subjects, including 2898 patients and 925 healthy volunteers have been exposed to rupatadine tablets in clinical studies at doses ranging from 2 mg to 100 mg with 2141 subjects exposed to RUPALL (rupatadine) 10 mg. In randomized controlled studies treatment duration ranged from one to twelve weeks. The most common adverse reactions reported with RUPALL 10 mg tablets were somnolence, headache, tiredness, asthenia, dry mouth, nausea, and dizziness. The majority of the adverse reactions observed in clinical trials were mild to moderate in severity and they usually did not require cessation of therapy.

A total of 337 patients 12 years and older were treated with RUPALL 10 mg tablets once daily up to at least 6 months with 121 patients exposed for at least 12 months.

Children 2-11 years of age:

A total of 306 children aged 2-11 years have been exposed to RUPALL Oral Solution in clinical studies. Considering the dose adjusted by body weight, 147 patients were exposed to a daily RUPALL dose of 2.5 mg and 159 subjects were exposed to RUPALL 5 mg. Period of exposure ranged from one to six weeks. The most common adverse reactions were related to central nervous system (CNS), headache and somnolence.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Allergic Rhinitis

Adults and Adolescents (12 years and older)

Two pivotal double-blind, randomized, controlled clinical studies were conducted in patients with seasonal allergic rhinitis and perennial allergic rhinitis. Together these two studies comprise a safety population of 902 patients aged 12 years and older (302 patients received RUPALL 10 mg, 307 placebo, 118 desloratadine 5 mg, and 175 cetirizine 10 mg). The treatment period was 4 to 12 weeks.

Somnolence and headache were common CNS adverse reactions in the controlled trials of patients 12 years or older in allergic rhinitis (Table 1). Somnolence was reported in 8.8% of RUPALL-treated patients compared to 2.0% of placebo patients. Headache was reported in 5.8% of RUPALL-treated patients compared to 4.9% of placebo patients.

Table 1: Treatment-Emergent Adverse Reactions (≥1%) Observed with RUPALL 10 mg Tablets and Placebo in Pivotal Allergic Rhinitis Studies

System Organ Class/Preferred Term	Placebo (N=307) n (%)	RUPALL 10 mg (N=294) n (%)
Nervous system disorders		
Somnolence	6 (2.0%)	26 (8.8%)
Headache	15 (4.9%)	17 (5.8%)
Dizziness	4 (1.3%)	4 (1.4%)
Investigations		
Blood creatine phosphokinase increased	5 (1.6%)	7 (2.4%)
ECG QT Prolonged	1 (0.3%)	3 (1.0%)
Gastrointestinal disorders		
Abdominal Pain	1 (0.3%)	5 (1.7%)
Vomiting	2 (0.7%)	3 (1.0%)
Epigastric Pain	2 (0.7%)	3 (1.0%)
General disorders and administration site conditions		
Tiredness	5 (1.6%)	4 (1.4%)

Children (2-11 years)

In one pivotal randomized, double-blind, placebo controlled study children aged 6-11 years with persistent allergic rhinitis were treated with RUPALL Oral Solution (n=180) or placebo (n=180), once daily for six weeks. There was one adverse reaction reported in a placebo patient, eczema.

Chronic Spontaneous Urticaria

Adults and Adolescents (12 years and older)

In the pivotal double-blind, randomized, controlled clinical study in chronic spontaneous urticaria, patients aged 12 years and older received RUPALL 10 mg tablets (n= 112) or placebo (n=113) once daily for up to 6 weeks. The study also consisted of a rupatadine 20 mg tablets treatment group (n=109).

The incidence of somnolence was higher in the placebo group (4.4%) compared to the RUPALL-treated group (2.7%). Incidences of adverse drug reactions for placebo which are comparable or greater than for the treatment group are not uncommon for allergy medications. Blood creatine phosphokinase was reported in 2.7% of RUPALL-treated patients compared to no reports for placebo (Table 2).

Table 2: Treatment-Emergent Adverse Reactions ($\geq 1\%$) Observed with RUPALL 10 mg and Placebo in Pivotal Urticaria Study

System Organ Class/ Preferred Term	Placebo (N=113) n (%)	RUPALL 10 mg (N=112) n (%)
Nervous system disorders		
Somnolence	5 (4.4%)	3 (2.7%)
Hypersomnia	1 (<1%)	2 (1.8%)
Headache	2 (1.8%)	1 (<1%)
Investigations		
Blood creatine phosphokinase increased	0	3 (2.7%)
Gastrointestinal disorders		
Dry mouth	1 (<1%)	2 (1.8%)
Nausea	2 (1.8%)	2 (1.8%)

Children (2-11 years)

In one pivotal randomized, double-blind, controlled study in patients aged 2-11 years of age with chronic spontaneous urticaria children received RUPALL Oral Solution (n=66), placebo (n=69) or desloratadine (n=71). Considering dosage adjustment by body weight, there were 47 patients treated with RUPALL 2.5 mg and 19 patients treated with RUPALL 5 mg, once daily for six weeks. Only one adverse reaction, headache, was reported in a child treated with RUPALL (Table 3).

Table 3: Treatment-Emergent Adverse Reactions ($\geq 1\%$) Observed with RUPALL Oral Solution and Placebo in Pivotal Urticaria Study in Children (2-11 years)

System Organ Class/Preferred Term	Placebo (N=69) n (%)	RUPALL (N=66) n (%)
Nervous system disorders		
Headache	1 (1.5%)	1 (1.5%)
Dizziness	1 (1.5%)	0
Metabolism and nutrition disorders		
Decreased appetite	1 (1.5%)	0
Gastrointestinal disorders		
Constipation	1 (1.5%)	0
Nausea	1 (1.5%)	0

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse reactions were observed less frequently (<1%) in the five pivotal clinical trials in allergic rhinitis and urticaria.

Blood and lymphatic system disorders: anemia

Cardiac disorders: palpitations

Ear and labyrinth disorders: motion sickness

Gastrointestinal disorders: diarrhoea, dry mouth, nausea

General disorders and administration site conditions: asthenia, pyrexia, thirsty, fatigue

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, gamma glutamyltransferase increase, alkaline phosphatase increase, weight increased

Metabolism and nutrition disorders: increased appetite

Musculoskeletal and connective tissue disorders: myalgia

Nervous system disorders: dysesthesia, hypoaesthesia, sedation, dizziness

Psychiatric disorders: depression, irritability, stupor

Skin and subcutaneous tissue disorders: eczema, rash, night sweats

Long-Term Safety:

Adults and Adolescents (12 years and older)

In two long-term safety studies of perennial allergic rhinitis, 337 patients 12 years and older were treated with RUPALL 10 mg tablets once daily up to at least 6 months with 121 patients exposed for at least 12 months. The most common adverse events (>5%) were headache, nasopharyngitis/common cold symptoms, somnolence, allergic rhinoconjunctivitis, gastroenteritis, catarrh, pharyngolaryngeal pain, acute tonsillitis,odynophagia, flu-like symptoms, fatigue, cough, and dysmenorrhoea.

Children (2-11 years)

The long term safety in children 2-11 years of age is limited to 6 weeks (See Clinical Trial Adverse Reactions).

Abnormal Hematologic and Clinical Chemistry Findings

Across all controlled and uncontrolled studies with RUPALL 10 mg, the incidence of blood chemistry findings reported as adverse events in RUPALL-treated subjects was similar to placebo.

There were six serious adverse events reported with rupatadine in clinical trials that were considered possibly related to study drug. Creatine phosphokinase increase was reported in three rupatadine-treated subjects (5 mg, 10 mg and 60 mg doses); all were asymptomatic and resolved. In two subjects treated with rupatadine 20 mg, aspartate aminotransferase and/or alanine aminotransferase increases were reported; all resolved.

Post-Market Adverse Drug Reactions

The post-marketing safety profile observed is consistent with that in controlled clinical trials. One case of torsade de pointes has been reported following the use of rupatadine when administered with concomitant medications known to have the potential for QT prolongation.

In post-marketing experience the following adverse reactions have been reported: arthralgia, atrial fibrillation, back pain, blood creatine phosphokinase increased, cough, dyspnoea, epistaxis, fatigue, headache, hypersensitivity reactions (including anaphylactic reactions, angioedema and urticaria), hypertension, increased appetite, myalgia, muscular weakness, nausea, off-label use, palpitations, QT prolongation, rhabdomyolysis, rash, somnolence, syncope, tachycardia, urticaria, weight increased, vertigo.

DRUG INTERACTIONS

Individual drug-drug interaction studies have been performed with rupatadine and ketoconazole, erythromycin, azithromycin, and fluoxetine. Particular care should be exercised when administering antihistamines, including rupatadine to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, ACTION AND CLINICAL PHARMACOLOGY).

Concomitant administration of rupatadine with known CYP3A4 inhibitors, ketoconazole or erythromycin, increased systemic exposure of rupatadine. The concomitant administration of rupatadine with azithromycin or fluoxetine did not result in any major changes in C_{max} and AUC for rupatadine and metabolites.

Drug-Drug Interactions

QTc-Prolonging Drugs:

The concurrent use of RUPALL with other QTc prolonging drugs is not recommended (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Inhibitors of CYP3A4:

The concomitant use of these drugs with RUPALL is not recommended (see

CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Drugs that Cause Electrolyte Depletion:

The use of RUPALL with drugs that can cause electrolyte imbalance is not recommended (see WARNINGS AND PRECAUTIONS).

Lorazepam

No clinically relevant CNS effects were observed when a single oral dose of lorazepam was co-administered with RUPALL 10 mg daily.

Effects of other drugs on rupatadine

Interaction with CYP3A4 inhibitors:

The concomitant administration of rupatadine 20 mg and ketoconazole increases the systemic exposure to rupatadine 10 times. Co-administration of rupatadine with ketoconazole and other potent CYP3A4 inhibitors (e.g. itraconazole, voriconazole, posaconazole, HIV protease inhibitors, clarithromycin, nefazodone) is not recommended (see CONTRAINDICATIONS).

The concomitant administration of rupatadine 20 mg and erythromycin increases the systemic exposure to rupatadine 2-3 times. Co-administration of rupatadine with erythromycin and other moderate CYP3A4 inhibitors (azithromycin, fluconazole, diltiazem) should be avoided (see WARNINGS AND PRECAUTIONS).

Effects of rupatadine on other drugs

Interaction with CNS depressants:

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

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 metabolized by the cytochrome P450 CYP3A4 isoenzyme, is unknown. For these reasons, RUPALL should be used with caution when it is coadministered with statins.

CYP3A4 substrates:

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 drugs.

Drug-Food Interactions

The concomitant administration of grapefruit juice increased the systemic exposure to rupatadine by 3.5 times. Grapefruit or grapefruit juice should not be taken simultaneously with RUPALL.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Lifestyle Interactions

RUPALL had no influence on the ability to drive and use machines. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction on rupatadine has been established.

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 (See DETAILED PHARMACOLOGY, Human Pharmacology). In sensitive patients, concurrent use of rupatadine with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Renal impairment

There is no clinical experience in patients with renal impairment. Therefore, the use of RUPALL (rupatadine) in patients with renal impairment is not recommended.

Hepatic impairment

There is no clinical experience in patients with hepatic impairment. Therefore, the use of RUPALL in patients with hepatic impairment is not recommended.

Pediatric (<2 years of age):

RUPALL should not be administered to children below 2 years of age. The efficacy and safety of RUPALL in this age group have not been studied.

Geriatrics (> 65 years of age)

No dosage adjustments are recommended in subjects > 65 years of age.

Recommended Dose and Dosage Adjustment

RUPALL Tablets (Adults and Adolescents 12 years of age and older):

Recommended Dose: 10 mg (1 tablet) once daily with or without food.

Maximum Daily Dose: 10 mg (1 tablet)

The maximum recommended daily dose is 10 mg (1 tablet) and should not be exceeded.

RUPALL Oral Solution (Children 2-11 years of age):

Body Weight of 10 to 25 kg

Recommended Dose: 2.5 mL (2.5 mg) once daily with or without food.

Maximum Daily Dose: 2.5 mL (2.5 mg)

Body Weight of >25 kg

Recommended Dose: 5 mL (5 mg) once daily with or without food.

Maximum Daily Dose: 5 mL (5 mg)

The maximum recommended daily dose should not be exceeded.

Administration

RUPALL Oral Solution is supplied with a 5 mL graduated plastic oral syringe which is to be inserted into the perforated stopper. With the bottle turned upside down, the syringe is filled to the prescribed dose. Wash the syringe after each use.

Missed Dose

If a dose of RUPALL Tablets or Oral Solution is missed, it should be taken as soon as possible, unless it is almost time for the next dose. A patient should not take two RUPALL doses at the same time to make up for a missed dose.

OVERDOSAGE

In a clinical safety study rupatadine at a 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Rupatadine is a second-generation antihistamine, long-acting histamine antagonist with selective peripheral H₁-receptor and platelet activating factor (PAF) antagonistic activities. Some of the metabolites (desloratadine and its hydroxylated metabolites) retain an antihistaminic activity and may partially contribute to the overall efficacy of the drug, maintaining activity for up to 24 hours.

Pharmacodynamics

The pharmacodynamics effects, both antihistamine and PAF-antagonist activities, of rupatadine were characterized by means of the inhibition of flares and wheals produced by intradermal injection of histamine and PAF in relationship to placebo and other gold standards. The specific inhibition of PAF was determined in blood on *ex vivo* platelet aggregation induced by PAF in healthy volunteers. The rapid absorption of rupatadine correlates with the onset of the antihistamine and PAF actions which occurs within 1 to 2 hours post-dose.

In addition, *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.

Cardiac Electrophysiology: A randomized, blinded, parallel, placebo and moxifloxacin controlled clinical trial was conducted in 160 healthy volunteers (gender balanced) randomized into four treatment groups: rupatadine therapeutic dose: 10 mg/day or suprathreshold dose: 100 mg/day, placebo or moxifloxacin 400 mg/day, each administered for five days. Moxifloxacin, a recognized standard for use as the positive control group produced an expected change in QTc duration of more than >10 msec.

On day 5 of treatment with the rupatadine 10 mg dose, a single statistically significant positive mean difference from placebo was observed at the 16 h time point: 6.1 ms (90% CI 2.5, 9.7).

On day 5 of treatment with the suprathreshold rupatadine 100 mg dose, statistically significant positive mean differences from placebo were observed at 2 of 13 time points, with a maximum mean difference from placebo of 6.8 ms (90% CI 3.5, 10.2) at 16 h. The time course was erratic (see, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, OVERDOSAGE).

Psychomotor Studies: In controlled clinical trials at the recommended dose of 10 mg once daily, the CNS safety profile of rupatadine was similar to placebo and the incidence of somnolence was not statistically different from placebo. Rupatadine at suprathreshold doses of 40 mg to 80 mg once daily produced CNS depression. Rupatadine 10 mg did not affect driving performance in a standard driving test. Nevertheless, care should be taken before driving or using machinery until the patient's individual reaction on rupatadine has been established (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, OVERDOSAGE).

No clinically relevant CNS effects were observed when a single oral dose of lorazepam co-administered with rupatadine 10 mg daily. As with other antihistamines, interactions with CNS depressants cannot be excluded (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, DRUG INTERACTIONS, OVERDOSAGE).

Combination of alcohol (0.8 g/kg) and rupatadine 20 mg produced more cognitive and psychomotor impairment than alcohol alone. Higher doses of rupatadine, in combination with alcohol, may induce cognitive and psychomotor deterioration as observed for hydroxyzine and cetirizine at therapeutic doses.

Pharmacokinetics

Absorption:

Rupatadine was rapidly absorbed after oral administration, with a time taken to reach the maximum plasma concentration (T_{max}) of 1 hour (median value). The maximum plasma concentration (C_{max}) obtained after single and repeated doses of 10 mg rupatadine were from 1.54 to 4.03 ng/mL and from 1.99 to 4.74 ng/mL respectively. Steady state was reached by the fifth day of therapy without extensive accumulation and the plasma concentration-time curve during a time dose interval (AUC_{τ}) ranged from 8.37 to 16.2 ng.h/mL. Pharmacokinetics of rupatadine was linear for a dose between 10 and 20 mg after single and repeated doses. The plasma concentration followed a bi-exponential drop-off with a mean elimination half-life after a single dose of 6.1 hours.

Table 4: Summary of Rupatadine's Pharmacokinetic Parameters Following a Single 10 mg Dose in Adults \geq 18 years

C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·h/mL)	T_{max} (h)	$t_{1/2}$ (h)	V_z/F (L)	Cl/F (L/h)
1.54 - 4.03	5.51 - 12.4	0.75 - 1	4.04 - 6.07	7567 - 11733	1036 - 2141

N=96 (age range 18-82 years)

Effect of Food: The influence of food was examined following administration of a 20 mg dose of rupatadine 10 mg tablets. Intake of a high-fat, high-calorie meal increased the systemic exposure (AUC) to rupatadine by about 23%. The systemic exposure to one of its active metabolites and to the main inactive metabolite was practically the same following administration of rupatadine with a high-fat, high-calorie meal (reduction in AUC of about 5% and 3%, respectively). The T_{max} for rupatadine was delayed by 1 hour. The maximum rupatadine concentration (C_{max}) was not affected by food intake. No food interaction study has been performed with rupatadine oral solution.

Distribution:

Plasma protein binding is 98.5-99.0% and apparently concentration-independent in the range studied. Metabolites did not exert any displacing effect. Rupatadine has a large apparent volume of distribution in healthy volunteers. The apparent volume of distribution (Vd/F) obtained after a repeated administration of a 10 mg dose was 9799 L.

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 piperidine nitrogen. *In vitro* metabolism studies in human liver microsomes indicate that rupatadine is mainly metabolized by the cytochrome P450 (CYP 3A4), with other CYP isoenzymes less involved, e.g., CYP2C9, CYP2C19 and CYP2D6. The main active metabolites were isolated and identified by mass and/or NMR spectrometry as desloratadine and hydroxylated forms of desloratadine.

Excretion:

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. 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.

Geriatrics: Following repeated dosing (7 days) in 12 healthy young (age 18-35) and 12 elderly (age 65-82) volunteers, $AUC_{0-\tau}$ and C_{max} were increased in elderly volunteers in relation to those observed in younger volunteers (C_{max} : 3.2 ng/mL vs 2.0 ng/mL; and $AUC_{0-\tau}$: 17.5 ng/mL.h vs 9.2 ng/mL.h, respectively). Furthermore, lower systemic clearance (Cl_{ss}/F) values were observed in elderly volunteers when compared to young volunteers (798.2 L/h vs 1556.2 L/h). The mean elimination half-life of rupatadine in elderly and young volunteers was 8.7 hours and 5.9 hours respectively. These differences were not observed in the metabolites analysed. 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.

Hepatic Insufficiency: There is no clinical experience in patients with hepatic insufficiency. Therefore, the use of RUPALL is not recommended in patients with impaired liver functions.

Renal Insufficiency: There is no clinical experience in patients with renal insufficiency. Therefore, the use of RUPALL is not recommended in patients with impaired renal functions.

STORAGE AND STABILITY

Keep out of reach and sight of children.

Tablets: Keep the blister in the outer carton in order to protect from light. Store at room temperature (15 to 30°C).

Oral solution: Store at room temperature (15 to 30°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

RUPALL (rupatadine) Tablet

Composition: Each RUPALL tablet contains 10 mg rupatadine (as 12.8 mg rupatadine fumarate) for oral administration. RUPALL Tablets are round, light salmon coloured tablets. Non-medicinal ingredients include: lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch, red iron oxide and yellow iron oxide. RUPALL Tablets are packaged in PVC/PVDC/aluminum blisters in boxes of 3 tablets (sample) and 30 tablets (commercial pack).

RUPALL Oral Solution

Composition: RUPALL Oral Solution contains 1 mg/mL rupatadine (as 1.28 mg/mL rupatadine fumarate) for oral administration.

RUPALL Oral Solution is a clear yellow liquid. Non-medicinal ingredients include: banana flavor, citric acid anhydrous, disodium phosphate anhydrous methyl parahydroxybenzoate, propylene glycol, purified water, quinoline yellow, saccharin sodium and sucrose.

RUPALL Oral Solution is packaged in 30 mL (sample) and 120 mL (commercial pack) amber-coloured PET bottles closed with a yellow-coloured polyethylene child-resistant closure with perforated stopper in a carton containing a 5 mL graduated plastic syringe for oral dispensing.

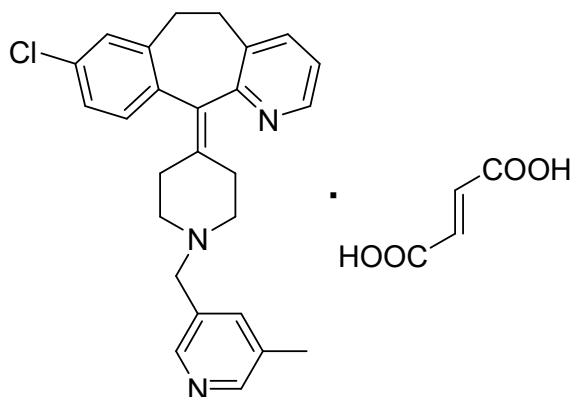
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	rupatadine (fumarate)
Chemical name:	8-Chloro-11-[1-[(5-methyl-3-pyridyl)methyl]piperidin-4-ylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine fumarate
Molecular formula and molecular mass:	C ₂₆ H ₂₆ ClN ₃ • C ₄ H ₄ O ₄
	Molecular mass of rupertadine fumarate: 532.03 Molecular mass of the rupertadine free base: 415.96

Structural formula:



Physicochemical properties:

Description:	White or slightly pinkish crystalline powder with a particle size mostly below 100 µm and non-hygroscopic.
Solubility:	Practically insoluble in neutral and basic media, slightly soluble in isopropanol, hexane, acetone, ethyl acetate, chloroform, dichloromethane and water and sparingly soluble in methanol, absolute ethanol, tetrahydrofuran and in a strongly acid medium (pH 1.4).
Melting Range:	195 – 201°C
Partition Coefficient:	logP (Octanol/Water) = 0.8

CLINICAL TRIALS

Efficacy in Seasonal Allergic Rhinitis (SAR) and Perennial Allergic Rhinitis (PAR)

Adult and Adolescent Patients 12 Years and Older

Study demographics and trial design

The efficacy of RUPALL (rupatadine) 10 mg tablets has been evaluated in 2 double-blind, randomized, parallel-group, multicenter, placebo and active-controlled pivotal clinical trials in adult and adolescent patients 12 years and older with symptoms of seasonal or perennial allergic rhinitis. One of these trials was 4 weeks in duration and the other 12 weeks in duration.

The trials included a total of 898 patients (367 males and 531 females) treated with 10 mg RUPALL, cetirizine 10 mg, desloratadine 5 mg tablets or placebo once daily. Of these patients, 291 received RUPALL 10 mg tablets. About 99% of patients were Caucasian in both trials.

Table 5: Summary of the Patient Demographics (ITT population) in Clinical Trials of RUPALL Tablets in Patients with Perennial Allergic Rhinitis and Seasonal Allergic Rhinitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
Study IC05RUP/4/03 SAR	Phase III: Double-blind, randomized, parallel-group, multicenter, placebo and active controlled design	RUPALL 10 mg, oral, QD	117	30.8 (16-67)	50.29% male 49.71% female
		Desloratadine: 5 mg oral, QD	117	32.0 (13-66)	
		Placebo oral, QD Tablet 4 weeks	122	31.8 (12-64)	
Study IC06RUP/3/04 PAR	Phase III: Double-blind, randomized, parallel-group, multicenter, placebo and active controlled design PAR	RUPALL 10 mg, oral, QD	183	28.58 (12-75)	34.69% male 65.31% female
		Cetirizine: 10 mg oral, QD	174	29.18 (12-70)	
		Placebo oral, QD Tablet 12 weeks	185	30.13 (12-69)	

ITT=intent-to-treat; PAR=Perennial Allergic Rhinitis; QD=once daily; SAR=Seasonal Allergic Rhinitis

In the pivotal studies, the primary efficacy variable was change from baseline in the total patient symptom-score (TSS).

TSS was comprised of the total nasal symptom score (TNSS) and the total non-nasal symptom score (TNNSS). Both reflective and instantaneous TSS were examined.

TNSS was based on the assessment of four nasal symptoms: rhinorrhea, nasal congestion, nasal itching, and sneezing, using a four point (0 [none] to 3 [severe]) scoring scale. Both reflective and instantaneous TNSS were examined.

TNNS included non-nasal symptoms: ocular pruritus, ocular redness, and tearing eyes (the latter being scored only in Study IC05RUP/4/03), and was assessed in a similar manner. Both reflective and instantaneous TNSS were examined.

Secondary efficacy endpoints included TNSS, TNNSS, and individual symptoms scores (reflective and instantaneous), overall condition of SAR and PAR, therapeutic response and assessment of life (Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]). The RQLQ was assessed only in Study IC06RUP/3/04 and included 7 domains (limitations in day-to-day activities, deterioration of sleep, non-nasal and non-ocular symptoms, practical problems, eye symptoms, nasal symptoms and emotional problems).

Study results

Seasonal Allergic Rhinitis (Study IC05RUP/4/03)

In the pivotal SAR trial, RUPALL 10 mg tablets resulted in a statistically significant reduction in the mean TSS (reflective evaluation) from baseline compared to placebo (p=0.03) over the 4-week treatment period (Table 6). At the same time, it did not differ from the active comparator (results not shown).

Table 6: Change from baseline in Reflective TSS (ITT)

TSS	Placebo n=122 mean (SD) (CI 95%)	RUPALL 10 mg n=117 mean (SD) (CI 95%)	P-value ¹
Baseline	14.01 (2.77) (13.51 / 14.51)	13.77 (2.68) (13.28 / 14.26)	
Final	8.79 (4.13) (8.05 / 9.53)	7.42 (3.70) (6.74 / 8.10)	
Change from baseline	-5.22 (4.21) (-5.97 / -4.47)	-6.35 (3.83) (-7.05 / -5.65)	p=0.028

¹ Tukey test

iTNSS for RUPALL 10 mg compared to placebo was statistically significant (p=0.012) and clinically meaningful (difference greater than 0.55 units). Both iTNNS and rTNNS for RUPALL compared to placebo were statistically significant (p=0.024, p=0.033 respectively).

Perennial Allergic Rhinitis (Study IC06RUP/3/04)

In the pivotal PAR trial, RUPALL 10 mg tablets resulted in a statistically significant reduction in the mean TSS (instantaneous evaluation) from baseline compared to placebo (p=0.008) over the 12-week treatment period. At the same time, the active comparator was not statistically significantly different than placebo (results not shown).

Table 7: Change from baseline in instantaneous TSS (ITT)

TSS	Placebo n=185 mean (SD) (CI 95%)	RUPALL 10 mg n=183 mean (SD) (CI 95%)	Test ¹
Baseline	8.96 (3.25) (8.49 – 9.43)	8.72 (2.90) (8.30 – 9.14)	
Final	5.48 (3.65) (4.95 – 6.01)	4.55 (2.90) (4.13 – 4.97)	
Change from baseline	-3.48 (3.62) (-4.01 – -2.95)	-4.17 (3.23) (-4.64 – -3.70)	p=0.008

¹ Tukey test

iTNSS at the end of the 12-week dosing interval demonstrated that RUPALL 10 mg resulted in statistically significant difference from placebo (p=0.008).

RUPALL was more effective in alleviating the burden of PAR as shown by the improvements in the RQLQ at last visit (week 12) compared to placebo.

Pediatrics Patients Aged 6 to 11 Years

Persistent Allergic Rhinitis (Study DC04RUP/3/08)

Study demographics and trial design

The efficacy of RUPALL 1 mg/mL Oral Solution has been evaluated in one double-blind, randomized, parallel-group, multicenter, placebo-controlled pivotal clinical trial in patients 6-11 years old with persistent allergic rhinitis ('persistent' symptoms occur more than 4 days per week, and more than 4 weeks) randomized to receive RUPALL 1 mg/mL Oral Solution or placebo once daily over a 6-week treatment period.

The trials included a total of 360 patients (217 males and 143 females) treated with RUPALL 1 mg/mL Oral Solution or placebo. About 49% of patients were Caucasian and 51% were Black, Asian or multiracial.

Table 8: Summary of the Patient Demographics (ITT population) in a Pediatric Clinical Trial of RUPALL Oral Solution in Patients with Persistent Allergic Rhinitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
Study DC04RUP/3/08 PAR	Phase III: randomized, double blind, placebo-controlled design	RUPALL 1 mg/mL solution, oral*	180	8.7 (6-11)	60% male 40% female
		Placebo: 1 mg/mL solution, oral 6 weeks	180	8.8 (6-12)	

ITT=intent-to-treat; PER= persistent allergic rhinitis; QD=once daily

*Dosage adjusted by body weight

The primary efficacy variable was the total 4 symptoms score (T4SS): (1) nasal congestion, (2) sneezing, (3) rhinorrhea, and (4) itchy nose, mouth throat and/or ears in the ITT population. The

primary end-point was defined as the difference between the mean of T4SS (sum of each individual symptoms score) over 28-day period (patient diary card reflective 24 hours assessment of all days including the same visit days with the investigator) and the baseline T4SS.

Secondary efficacy endpoints included total T4SS after 42 days of treatment, total symptoms score of patient reflective symptoms (T5SS: nasal congestion, sneezing, rhinorrhea, itchy nose / mouth throat and/or ears, and itchy – watery and red eyes) during 28 and 42 days of treatment, individual symptoms scores (reflective and instantaneous) and assessment of life (Paediatric Rhinoconjunctivitis Quality of Life Questionnaire [PRQLQ]). The PRQLQ assessed 5 domains (limitations in day-to-day activities, nasal symptoms, ocular symptoms, other symptoms, practical problems).

Study results

RUPALL 1 mg/mL Oral Solution resulted in statistically significant (p=0.018) improvement compared to placebo in the change of T4SS from baseline over the 4-week treatment period which represented a 43% reduction for RUPALL in comparison with the 35% with placebo. Similar results were obtained for the secondary endpoint of efficacy change in T4SS after 42 days of treatment compared to placebo (-3.3 vs. -2.7).

Table 9: Change from baseline in the T4SS over 28-day period (ITT)

Variable (mean (SD)) (lower/upper 95% CI)	Placebo N=180	RUPALL solution N=180	Test*
T4SS at baseline	7.23 (1.05) 7.07 / 7.38	7.23 (1.10) 7.07 / 7.40	
T4SS at day 28	4.67 (2.14) 4.35 / 4.98	4.17 (2.25) 3.84 / 4.50	
Change in T4SS	-2.56 (1.95) -2.84 / -2.27	-3.06 (2.08) -3.37 / -2.76	p=0.018

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; SD = standard deviation; T4SS = total 4 symptom score

*ANCOVA

RUPALL 1 mg/mL Oral Solution was superior to placebo in the change from baseline in the Total Symptoms Score (T5SS) of patient reflective symptoms at day 28 for the ITT population.

RUPALL 1 mg/mL Oral Solution lowered the mean PRQLQ values compared with placebo after 28 days (33.3% vs. placebo 22.72%) and at 42 days (42.9% vs. placebo 31.8%).

Efficacy in Chronic Spontaneous Urticaria

Adult and Adolescent Patients Aged 12 Years and Older (Study IC02RUP/II/02 and IC010RUP/3/04)

Study demographics and trial design

The efficacy of RUPALL 10 mg tablets was evaluated in two randomized, double-blind, parallel-group, multicenter, placebo-controlled clinical trials in adult and adolescent patients 12 years and older in the treatment of Chronic Spontaneous Urticaria (CSU). The two trials included one 4-week dose ranging trial (IC02RUP/II/02) and one 6-week pivotal efficacy trial (IC010RUP/3/04).

Table 10: Summary of the Patient Demographics (ITT population) in Clinical Trial of RUPALL Tablets in Patients with Chronic Spontaneous Urticaria

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
Study IC02RUP/II/02 CSU	Phase II: Double-blind, randomized, multicenter, parallel-group, placebo-controlled	Rupatadine 5 mg, oral, QD	64	36.3 (14-62)	28% male 72% female
		RUPALL 10 mg, oral, QD	66	39.2 (16-64)	
		Rupatadine 20 mg, oral, QD	64	36.3 (13-65)	
		Placebo, oral, QD Tablet 4 weeks	64	37.5 (16-71)	
Study IC010RUP/3/04 CSU	Phase III: Double-blind, randomized, multicenter, parallel-group, placebo-controlled	RUPALL 10 mg, oral, QD	110	40.2 (13-65)	32% male 68% female
		Rupatadine 20 mg, oral, QD	108	37.6 (13-65)	
		Placebo, oral, QD Tablet 6 weeks	111	35.8 (12-64)	

ITT=intent-to-treat; QD=once daily

These clinical trials included a total of 587 patients (177 males and 410 females) with CSU treated with rupatadine 5 mg, 10 mg, 20 mg tablets, or placebo. Of these patients, 176 received RUPALL 10 mg tablets once daily. About 98% of patients were Caucasian.

Pruritus severity and the number of wheals were recorded by patients in daily diary cards in the morning and at bedtime. The severity of pruritus was assessed by scoring on a 5-point scale of 0–4 with 0 = none; 1 = mild, not annoying or troublesome; 2 = moderate, annoying or troublesome; 3 = severe, very annoying, substantially interfering with sleep/daily activities and 4 = very severe warranting doctor visit. Similarly, the number of wheals was also scored on a 5-point scale with 0= no wheal; 1= 1–5 wheals; 2 = 6–15 wheals; 3= 16–25 wheals; 4 = ≥25 wheals.

The primary efficacy endpoint for both studies was the change from baseline in mean pruritus score (MPS) over the 4-week treatment period.

Secondary efficacy endpoints in IC010RUP/3/04 study were change from baseline in MPS over the 6-week treatment period, change from baseline in mean number of wheals (MNW) score, the mean of total symptoms score (MTSS; calculated as the sum of MPS and MNW); Dermatology Life Quality Index (DLQI; a measure of QoL) and visual analogue scale (VAS), over the 4- and 6-week treatment periods. The DLQI assessed 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment). Overall efficacy was also assessed as a secondary outcome after treatment for 2, 4 and 6 weeks by the patient and investigator. Secondary efficacy endpoints in IC02RUP/II/02 study were change from baseline in MNW over the 4-week treatment period, change from baseline in the mean of total symptoms score (MTSS; calculated as the sum of MPS and MNW) and changes from baseline over the 4 weeks on treatment in the interference with daily activities and sleep mean scores

Study results

IC02RUP/II/02

RUPALL 10 mg was statistically better than placebo in reducing the MPS over a 4-week (p<0.001) in the per-protocol (PP) population.

Table 11: Change in MPS over the 4-week treatment period (PP)

MPS	Placebo Mean (SD) CI95%	RUPALL 10 mg Mean (SD) CI95%	Test ¹
PP	N=64	N=66	
4 weeks			
Baseline MPS	2.48 (0.51) (2.35 - 2.61)	2.44 (0.52) (2.31 - 2.57)	
MPS	1.33 (1.15) (1.04 - 1.62)	0.93 (0.89) (0.71 - 1.14)	p<0.001
Change MPS	-1.15 (0.93) (-1.38 - -0.92)	-1.51 (0.78) (-1.70 - -1.31)	p<0.001
% Change vs. baseline	-46%	-62%	

MPS = mean pruritus score; PP = per-protocol; SD = standard deviation

¹ ANOVA

IC010RUP/3/04

RUPALL 10 mg was statistically better than placebo in reducing the MPS over a 4-week (p=0.001) and 6-week treatment period (p=0.020) in the ITT population.

Table 12: Change in MPS over the 4- and 6-week treatment period (ITT)

MPS	Placebo Mean (SD) CI95%	RUPALL 10 mg Mean (SD) CI95%	Test
ITT	N=111	N=110	
4 weeks			
Baseline MPS	2.54 (0.46) (2.45 - 2.63)	2.47 (0.45) (2.39 - 2.56)	p<0.001 ¹
MPS	1.41 (0.82) (1.26 - 1.56)	1.05 (0.82) (0.90 - 1.21)	p<0.001 ²
Change MPS	-1.13 (0.71) (-1.26 - -1.00)	-1.42 (0.73) (-1.56 - -1.28)	
% Change vs. baseline	-44.9%	-57.5%	
ITT	N=111	N=110	
6 weeks			
Baseline MPS	2.54 (0.46) (2.45 - 2.63)	2.47 (0.45) (2.39 - 2.56)	p=0.0003 ¹
MPS	1.30 (0.84) (1.14 - 1.46)	1.00 (0.85) (0.84 - 1.16)	
Change MPS	-1.24 (0.74) (-1.38 - -1.10)	-1.47 (0.76) (-1.61 - -1.33)	

ITT = intent-to-treat; MPS = mean pruritus score; PP = per-protocol; SD = standard deviation

¹ ANOVA

² ANCOVA

RUPALL 10 mg was statistically better than placebo in reducing the MNW score from baseline in the ITT population over the 4-week treatment period (p=0.015).

Pediatrics Patients Aged 2 to 11 Years (Study DC02/RUP/III/09)

Study demographics and trial design

The efficacy of RUPALL 1 mg/mL Oral Solution has been evaluated in a double-blind, randomized, parallel-group, multicenter, placebo-controlled and active-controlled pivotal clinical trial in pediatric patients 2-11 years old in the treatment of CSU over a 6-week treatment period.

Table 13: Summary of the Patient Demographics (ITT population) in Clinical Trials of RUPALL Oral Solution in Patients with Chronic Spontaneous Urticaria

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
Study DC02/RUP/III/09 CSU	Phase III: Multicentre, randomized, double blind, placebo and active controlled design	RUPALL: 1 mg/mL*, oral, QD	63	5.58 (2.04 – 11.65)	52.26% male 47.74% female
		Desloratadine: 0.5 mg/ mL, QD	69	6.08 (2.06 – 11.74)	
		Placebo, oral, QD Solution 6 weeks	67	6.09 (2.03 – 11.32)	

ITT=intent-to-treat; QD=once daily

*Dosage adjusted by body weight

The primary efficacy endpoint was the change from baseline in the mean adapted cumulative urticaria activity score (UAS7) over the 6-week treatment period. The UAS is calculated on a daily basis by means of the 24 hour reflective symptoms (wheals and pruritus).

Secondary efficacy endpoints were change in the adapted mean number of wheals (MNW) score and mean pruritus score (MPS) over the 6-week treatment period; investigator's, parent's and patient's global assessment of efficacy using a visual analogue scale (VAS); progression of the adapted UAS, MNW and MPS over the 6-week treatment period evaluated week by week; analysis of responder patients profile; use of rescue medication, onset of action (measured by UAS7) and assessment of life (Children Dermatology Life Quality Index [CDLQI]). The CDLQI assessed 6 domains (symptoms/feelings, daily activities, school/holiday activities, personal relations, sleep and treatment).

Study results

RUPALL 1 mg/mL Oral Solution was superior to placebo, both for the change in UAS7 ($p < 0.001$) and the percentage of change in UAS7 over the 6-week treatment period. Change in UAS7 from baseline (of greater than 9.5 to 10.5 units) over the 6-week treatment period was clinically meaningful with RUPALL 10 mg compared to placebo.

Table 14: Change in Adapted UAS7 over 6-week (ITT)

Variable	Placebo (mean (SD)) CI95%	RUPALL (mean (SD)) CI95%	Desloratadine (mean (SD)) CI95%	Test (ANCOVA)
ITT population	67	63	69	
UAS7 Baseline	20.45 (6.10) (18.96 – 21.94)	22.06 (7.93) (20.06 – 24.06)	22.29 (7.21) (20.56 – 24.02)	
UAS7 Final	15.05 (9.74) (12.67 – 17.43)	10.39 (10.25) (7.81 – 12.97)	11.97 (9.68) (9.64 – 14.30)	
Change UAS7	-5.55 (7.52) (-7.33 - -3.67)	-11.77(8.68) (-13.96 - -9.58)	-10.55 (9.58) (-12.85 - -8.25)	p< 0.001
% Change UAS7	-30.29 (41.37) (-40.38 - -20.20)	-55.83 (38.15) (-65.44 - -46.22)	-48.43 (44.07) (-59.02 - -37.84)	p= 0.001

ANCOVA = analysis of covariance; ITT = intent-to-treat; SD = standard deviation; UAS7 = Urticaria Activity Score of the 7 days

RUPALL 1 mg/mL Oral Solution effect was superior to placebo, both for change MNW and % change MNW. The mean greatest change of MNW obtained with RUPALL was -56.7%, and with placebo -22.7%. Similar results were obtained for MPS.

RUPALL provided greater health-related quality of life improvement than placebo after 42-days treatment period.

DETAILED PHARMACOLOGY

Nonclinical Pharmacology

Extensive studies both *in vitro* and *in vivo* have demonstrated the antagonist activity of rupatadine towards both histamine H₁ and PAF receptors, as well as its potential anti-allergic effect.

The antihistamine activity of rupatadine has been demonstrated in five different *in vitro* models, both functional (rabbit and guinea pig H₁ receptor models) and binding (guinea pig ileum tests). The studies revealed that the binding of rupatadine to the H₁ receptor is time-dependent and its behavior is pseudo-irreversible, as described for many second-generation antihistamines.

The PAF antagonistic activity of rupatadine has been demonstrated in six functional and binding studies in rabbit and dog *in vitro* models. Results show that rupatadine causes a non-competitive displacement of the selective ligand [³H]-WEB-2086 from PAF receptors in platelets. It inhibits PAF-induced platelet aggregation.

The dual H₁-antihistamine and PAF-antagonist activity of rupatadine has also been demonstrated in ten studies in different *in vivo* models in mouse, rat, guinea pig and dog.

The anti-allergic activity of rupatadine was studied in six *in vivo* studies performed in mouse, rat, guinea pig and dog models. Rupatadine was shown to strongly inhibit type I hypersensitivity reactions in different anaphylaxis models, with a prolonged duration of action. The potential of rupatadine to inhibit type III hypersensitivity reactions was also demonstrated.

The effects of rupatadine were assessed on several different systems or functions, including the cardiovascular, renal, and respiratory systems, the central and autonomous nervous systems, coagulation, gastrointestinal motility and behavior.

In vitro and *in vivo* studies showed low potential of anticholinergic effects for rupatadine. The effect of rupatadine on the CNS is similar to that of second-generation antihistamines, known as “non-sedative” antihistamines.

In vitro cardiovascular studies showed a low potential of rupatadine for effects on action potential duration or for QT prolongation due to HERG channel blockade. Also, in *in vivo* studies no electrocardiographic effects were observed in any of the animal species tested (dogs, guinea pigs and rats) at doses of rupatadine 100 times or more than the recommended dose in humans. Generally mild and/or transient changes were reported in cardiovascular parameters following iv administration in rats (30 mg/kg), guinea pigs (30 mg/kg) and dogs (2 and 20 mg/kg) although a substantial increase in cardiac contractility occurred following a single iv dose at 20 mg/kg in dogs.

Human Pharmacology

The human pharmacodynamic effects, both antihistamine and PAF-antagonist activities of rupatadine, were investigated in terms of its ability to inhibit the flares and wheals produced by intradermal injection of histamine and PAF in comparison to placebo and other reference compounds. These studies were complemented by a nasal challenge test with a specific allergen in atopic volunteers.

The percentage inhibition of both PAF and histamine induced flares lagged behind mean plasma levels of rupatadine and its metabolite, desloratadine. The inhibition was significantly higher in comparison to placebo for 10 mg and higher doses and the percentage and duration of inhibition increased with dose. The maximum mean percentage inhibition occurred between two and three hours after maximum mean plasma rupatadine and desloratadine concentrations and remained high (>60%) even when mean rupatadine and desloratadine in plasma had dropped to negligible levels (<0.5 ng/mL).

In a placebo-controlled cross-over study, the effect of rupatadine, placebo or a reference compound on the overall reduction of PAF-induced nasal symptoms in allergic rhinitis patients was measured. Rupatadine caused a significant reduction of T4SS AUC compared to placebo showing PAF inhibitory effects of rupatadine on human nasal airways.

Table 15: Acute Toxicity of Rupatadine and Hydroxylated Metabolite (3-Hydroxydesloratadine)

Species and Strain	Method of Administration	Dose (mg/kg)		LD ₅₀ values (mg/kg)
		Rupatadine	Metabolite	
Mouse/Swiss	Oral gavage	500, 2000	-	>500
		-	2000	>2000
	Intraperitoneal	50, 200, 500	-	>200 (males) >50 (females)
	Intravenous	-	25, 50, 200	>50
Rat/Sprague-Dawley	Oral gavage	2000	-	>2000
		-	2000	>2000
	Intraperitoneal	25, 50, 200	-	>200
	Intravenous	-	25, 50, 200	>50

Repeated-Dose Toxicity

Repeated-dose toxicity of rupatadine was assessed in rats and Beagle dogs after oral administration. An overview of these studies is provided in Table 16.

Table 16: Repeated-Dose Toxicity Studies with Rupatadine and Hydroxylated Metabolite (3-Hydroxydesloratadine)

Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)		NOAEL (mg/kg/day)	Animal to human exposure ratios ¹ for Rupatadine
			Rupatadine	Metabolite		
Rat/Crl:CD (SD) BR / VAF plus	Oral gavage	13-week	3, 30, 120	-	30	118-145
Rat/Crl:CD (SD) BR / VAF plus		26-week	3, 30, 120	-	30	
Rat/Sprague Dawley	Oral gavage	4-week	-	3, 30, 120	120	-
Dog/Beagle	Oral gavage	13-week	1.25, 7, 40	-	7	-
		26-week	1, 5, 20	-	20	
Dog/Beagle	Oral gavage	39-week	1.25, 7, 40	-	40	1750-800

¹ AUC₍₀₋₂₄₎ ratio; Safety ratios were calculated at NOAEL which were 30 mg/kg/day for the rat and 40 mg/kg/day for the dog. Human dose was 10 mg/day.

The most significant results found at the high dose in a subchronic toxicity study in rats treated by oral gavage at doses of 3, 30 and 120 mg/kg/day for 13 weeks were a decrease in body weight gain in males raised leukocyte count and urine volume in females, and an increase in liver weight in both sexes. The no observed level (NOEL) was between 30 mg/kg/day for males and 3 mg/kg/day for females and it was concluded that the NOAEL was 30 mg/kg/day. Systemic exposure (AUC-based) measured at 30 mg/kg/day in the rat was 118 to 145-fold and 210 to 319-fold higher than therapeutic levels of rupatadine and hydroxylated metabolite (desloratadine) at the recommended human daily dose of 10 mg, respectively.

In a chronic study in rats treated by oral gavage at doses of 3, 30 and 120 mg/kg/day for 26 weeks, the main findings at the high dose were reduction in weight gain, rise in leukocyte

(females) and neutrophil counts (both sexes), fall in haemoglobin concentration (males), increase in plasma creatinine accompanied in females by slight increase in BUN, increase in total proteins, and increase in urine volume and decrease in urine specific gravity. Effects on clinical pathology in the intermediate dose were restricted to increase in total proteins in males and the same changes reported in the urine as in the high dose group. Several macroscopic and histopathological changes were observed at 120 mg/kg/day in both sexes. The histopathological changes observed at the intermediate dose were of lesser magnitude and were confined to the liver of male and female rats and mesenteric lymph nodes of male rats. Changes at 3 mg/kg/day were confined to the liver of male rats. The no observed adverse effect level (NOAEL) was set at 30 mg/kg/day.

Rupatadine was administered orally to Beagle dogs at doses of 1.25, 7 and 40 mg/kg/day for 13 weeks. The clinical signs observed were hyperactivity, aggressiveness and anxiety at the 7 mg/kg/day dose in males and at the 40 mg/kg/day dose in both sexes with increased severity. The levels of alkaline phosphatase (males) and alanine transaminase (both sexes) were slightly raised at the high dose. Weight increase in females was reduced at a dose of 7 mg/kg/day and in both sexes at a dose of 40 mg/kg/day. Kidney and liver weights standardized by body weight were raised in males at the intermediate and high dose. The NOAEL was concluded to be 7 mg/kg/day.

In the chronic toxicity studies Beagle dogs were treated orally at doses of 1, 5, 20 and 1.25, 7, 40 mg/kg, day for 26 weeks and 39 weeks, respectively. At the doses of 5 and 20 mg/kg/day, rupatadine produced clinical signs similar to those observed in the 13-week trial (hyperactivity, elevated respiration rate, salivation, excessive urine production). Due to their transient nature these effects were not regarded as toxicologically important. Slight changes were also observed in haematology (increase in erythrocytes) and biochemistry (increase in alkaline phosphatase). The values were, however, still within the normal range and were therefore not regarded as toxicologically important. The 26-week study concluded that the NOAEL was 20 mg/kg/day. At doses of 7 and 40 mg/kg/day, slightly reduced body weight and increased plasma alkaline phosphatase levels were observed. Increased body weight-related liver weights were also observed at the end of the treatment period with 40 mg/kg/day. These changes were reversible, following a 28 day treatment free period and were not considered adverse in the absence of macroscopic or microscopic findings. The 39-week study concluded that the NOAEL was 40 mg/kg/day. Systemic exposure (AUC-based) measured at 40 mg/kg/day in the dog was 800 to 1750-fold and 1280 to 1345-fold higher than therapeutic levels of rupatadine and hydroxylated metabolite (desloratadine) at the recommended human daily dose of 10 mg, respectively.

Study in Juvenile Animals

A toxicity study was performed in juvenile Crl:CD (SD) rats to investigate the effects of rupatadine (4.5 and 30 mg/kg/day) and rupatadinium succinic acid (RSA) impurity on the juvenile development of the rat following once daily oral (gavage) administration to pups from Day 22 to at least Day 50 of age.

Decreased activity and partially closed eyes were observed for both sexes treated with rupatadine 30 mg/kg/day with or without RSA impurity. In the same two groups, treatment-related microscopic findings were recorded in the vagina, ovaries and mammary tissue in females. For

all other parameters, there were no toxicologically significant changes considered to be related to treatment. There were no substantive differences between the toxicity profile of rupatadine and rupatadine that contained 5 % RSA impurity. The effects on the reproductive system of females were suggestive of an alteration in the normal oestrogen/progesterone ratio, possibly secondary to increased oestrogen catabolism related with induction of hepatic biotransformation enzymes, which may in turn affect levels of circulating hormones. Therefore, these changes were considered not to be adverse in nature. The NOAEL was established at 30+1.5 mg/kg/day (rupatadine + RSA impurity) or 30 mg/kg/day rupatadine alone. The rupatadine dose of 30 mg/kg/day in rats is 20 times higher than the dose recommended in children (2.5 mg in a child of 10 kg average body weight) on a mg/m² basis.

Carcinogenicity

Two long-term carcinogenicity studies were carried out in two species, the mouse (at least 78 weeks) and the rat (at least 104 weeks) (Table 17).

Table 17: Overview of Carcinogenicity Studies with Rupatadine

Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)	Animal to human exposure ratios ¹
Mouse/NMRI, Hannover-derived, outbreed, SPF quality	Oral (feeding)	78-week	6, 25, 100/60/40	1-3
Rat/Wistar, Hannover derived, outbreed, SPF quality	Oral (feeding)	104-week (oncogenicity)	2.5, 10, 40	72-94

¹ AUC₍₀₋₂₄₎ ratio; Safety ratios were calculated for the doses of 25 mg/kg/day (mice) and 40 mg/kg/day (rat). Human dose was 10 mg/day.

In the mouse study, due to increased male mortality at the high dose, the dose was reduced in males to 60 mg/kg/day from Week 34 to 55, and to 40 mg/kg/day from Week 56 until the end of the study. For females the dose was reduced to 60 mg/kg/day from Week 56 until the end of the study. Treatment-related clinical signs were observed only at the high dose. The most frequent, especially among male animals, were the presence of wrinkly skin, hunched posture, cachexia and swollen abdomen. Most of the animals displaying these signs died or were sacrificed in extremis within a week of the appearance of the signs. The primary cause of death was constipation, with major intestinal distension and accumulation of faeces. This effect was probably due to excessive pharmacological activity of rupatadine.

There was no increase in the incidence and severity of neoplastic lesions in the treated mice compared with the controls. The most frequent were recorded in the lungs, haemolymphoreticular system, ovaries, adrenals and Harderian glands, and are common in animals of this strain and age.

In conclusion, rupatadine did not show any carcinogenic potential under the study conditions in mice at doses up to 40 (males) or 60 (females) mg/kg/day. Systemic exposure at these dose levels was not measured. However, systemic exposure (AUC-based) measured at the mid dose

(25 mg/kg/day) was 1 to 3-fold and 70 to 118-fold higher than therapeutic levels of rupatadine and hydroxylated metabolite (desloratadine), respectively.

In the rat study some non-neoplastic observations were recorded at 40 mg/kg/day consisting of an increased incidence of *foci* in the lungs (likely attributed to aspiration of rupatadine powder from the diet), correlated with alveolar histiocytosis seen in the histological exam, and the appearance of centrilobular hypertrophy of liver cells together with a mainly macrovesicular accumulation of lipids. A greater incidence of diffuse hypertrophy of thyroid follicular cells and adenomas of thyroid follicular cells was observed at the high dose. These findings could be attributed to non-neoplastic mechanisms and are species-dependent. Other non-neoplastic or neoplastic lesions observed were the same in type and incidence than those recorded in control rats of the strain and age studied.

In conclusion, rupatadine did not show any carcinogenic potential under the study conditions in rats at doses up to 40 mg/kg/day. Systemic exposure (AUC-based) measured at 40 mg/kg/day was 72 to 94-fold and 119 to 277-fold higher than therapeutic levels of rupatadine and hydroxylated metabolite (desloratadine), respectively.

Mutagenicity

Genotoxicity of rupatadine has been assessed in both *in vitro* and *in vivo* studies. Two metabolites were also tested in a reverse mutation assay (Table 18).

Table 18: Overview of Genotoxicity Studies with Rupatadine and Metabolites

Species and Strain	Method of Administration	Doses	Outcome
<i>In vitro</i>			
<i>Salmonella typhymurium</i> TA1535, TA1537, TA1538, TA 98, T100	<i>In vitro</i>	0.32, 1.6, 8, 40, 100, 150, 200 µg/plate	Negative
<i>Salmonella typhymurium</i> TA1535, TA 97a, TA98, TA100, TA102	<i>In vitro</i>	25, 50, 100, 200, 400 µg/plate (3-hydroxydesloratadine)	Negative
<i>Salmonella typhymurium</i> TA1535, TA 97a, TA98, TA100, TA102	<i>In vitro</i>	20, 60, 200, 600, 2000 µg/plate (O-glucuronide conjugate of 3-hydroxydesloratadine)	Negative
<i>Escherichia coli</i> WP2 uvrA and WP2 uvrA pkM 101	<i>In vitro</i>	39.06, 78.125, 156.25, 312.5, 625, 1250 and 2500 µg/plate	Negative
Human lymphocytes	<i>In vitro</i>	without S9: 2, 10, 20 µg/mL with S9: 6, 30, 60 µg/mL	Negative
<i>In vitro</i>			
Mouse lymphoma L5178Y cells	<i>In vitro</i>	without S9: 1, 3, 5, 10, 20, 25 and 30 µg/mL with S9: 1, 3, 5, 10, 20, 30 40, 50, and 60 µg/mL	Negative
<i>In vivo</i>			
Mouse / CD1	Oral Gavage	125, 200, 320 mg/kg	Negative

Rupatadine did not show any genotoxic potential in the battery of tests performed. None of metabolites showed mutagenic potential in the reverse mutation assay.

Reproductive Toxicology

Reproductive toxicology was assessed in several studies in rats and rabbits (Table 19).

Table 19: Overview of Reproductive and Developmental Toxicity Studies

Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg/day)	NOAEL (mg/kg/day)
<i>Fertility and Early Embryonic Development to Implantation</i>				
Rat /rl:CD(SD)BR/VAF plus	Oral Gavage	M: 61 days before mating. F: From Day 15 a.c. to Day 17 of pregnancy	5, 25, 120	5 (female fertility and embryo-foetal developmental toxicity) 25 (male fertility) 120 (teratogenic potential)
<i>Effects on Embryofetal Development</i>				
Rabbit / New Zealand White	Oral Gavage	F: from Day 6 to 18 of gestation (13 days)	5, 25, 100	100 (embryo-foetal developmental toxicity and teratogenic potential)
<i>Effects on Pre- and Postnatal Development, Including Maternal Function</i>				
Rat / OFA (SD) IOPS-Caw Sprague-Dawley	Oral Gavage	F: from Day 6 of pregnancy to Day 20 post-partum	5, 25, 120	5 (peri- and post-natal development)

a.c. = ante coitus

Studies of fertility and embryonic development in the rat showed a significant reduction of male and female fertility at the dose of 120 mg/kg/day, which resulted in a C_{max} of rupatadine 113 times greater than that obtained after the administration of 10 mg/day in humans. Foetal toxicity (growth delay, incomplete ossification, minor skeletal findings) was reported in rats at maternotoxic dose-levels only (25 and 120 mg/kg/day). No abnormalities in foetal structure or macroscopic changes in external or visceral appearance were observed. The NOAEL for female fertility and embryo-foetal developmental toxicity was determined at 5 mg/kg/day in rats, which is 25 times the proposed therapeutic dose in humans in terms of mg/kg and 4 times in terms of mg/m^2 .

In the rabbit, doses of 5, 25 and 100 mg/kg/day were administered orally to pregnant does during the period of organogenesis (Days 6 to 18 of gestation). At the high dose slight maternal toxicity was observed but there was no evidence of embryo-foetal toxicity. At the intermediate and low doses no maternal or embryo-foetal toxicity was observed. The NOAEL was determined at 100 mg/kg/day in rats, yielding a C_{max} of 49 times higher, than that measured in humans at the 10 mg/day therapeutic dose.

A peri- and post-natal toxicity study in rat was designed to investigate the effects of rupatadine at doses of 5, 25 and 120 mg/kg/day administered orally on embryonic, foetal and post-natal development, following the administration of these doses to gravid animals from Day 6 of gestation, during lactation and until Day 20 post-partum. The high dose caused maternal toxicity, characterized by poor clinical condition when giving birth, prolonged birth times, a reduction in body weight gain and a decrease in food consumption. It also caused a reduction in litter weight at birth and slow development of the offspring, due to poor or absent maternal care. At the intermediate dose only slight maternal toxicity was observed. No maternal toxicity or litter effects were observed at the low dose (NOAEL).

REFERENCES

- Donado E, Izquierdo I, Pérez I, García O, Antonijoan RM, Gich I, et al. No cardiac effects of therapeutic and suprathreshold doses of rupatadine: results from a 'thorough QT/QTc study' performed according to ICH guidelines. *Br J Clin Pharmacol* 2010; 69(4):401–410 (**Study IC012RUP/1/04**)
- Dubertret L, Zalupca L, Cristodoulo T, Benea V, Medina I, Fantin S, et al. Once-daily rupatadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study. *Eur J Dermatol* 2007; 17 (3): 223-228. (**Study IC02RUP/II/02**)
- Fantin S, Maspero J, Bisbal C, Agache I, Donado E, Borja J, et al. A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. *Allergy* 2008; 63:924-931 (**Study IC06RUP/3/04**)
- Gimenez-Arnau A, Pujol RM, Ianosi S, Kaszuba A, Malbran A, Poop G, et al. Rupatadine in the treatment of chronic idiopathic urticaria: A double-blind, randomized, placebo-controlled multicentre study. *Allergy* 2007; 62:539-546 (**Study IC010RUP/3/04**)
- Lukat KF, Rivas P, Roger A, Kowalski ML, Botzen U, Wessel F, et al. A direct comparison of efficacy between desloratadine and rupatadine in seasonal allergic rhinoconjunctivitis: a randomized, double-blind, placebo-controlled study. *Journal of Asthma and Allergy* 2013; 6:31-39 (**Study IC05RUP/4/03**)
- Muñoz-Cano R, Valero A, Izquierdo I, Sánchez-López J, Doménech A, Bartra J, et al. Evaluation of nasal symptoms induced by platelet activating factor, after nasal challenge in both healthy and allergic rhinitis subjects pretreated with rupatadine, levocetirizine or placebo in a cross-over study design. *Allergy Asthma Clin Immunol.* 2013 Nov 1;9(1):43. (**Study DC03/RUP/I/08**)
- Potter P, Maspero JF, Vermeulen J, Barkai L, Németh I, Baillieu RA, et al. Rupatadine oral solution in children with persistent allergic rhinitis: A randomized, double-blind, placebo-controlled study. *Pediatric Allergy and Immunology* 2013; 24:144-150 (**Study DC04/RUP/3/08**)
- Potter P, Mitha E, Barkai L, Mezei G, Santamaria E, Izquierdo I, et al. Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2-11 years. *Pediatric Allergy and Immunology* 2016; 27:55-61 (**Study DC02/RUP/III/09**)
- Valero A, de la Torre F, Castillo JA, Rivas P, del Cuvillo A, Antépara I et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in Spain. *Drug Saf.* 2009;32(1):33-42. (**Study IC01/RUP/IV/02**)

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**PrRUPALL™
Rupatadine Tablets
10 mg rupatadine (as rupatadine fumarate)**

Read this carefully before you start taking **RUPALL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RUPALL**.

What is RUPALL used for?

RUPALL Tablets are used in patients 12 years of age and older, to treat the symptoms of:

- **Seasonal Allergic Rhinitis** (hay fever)
- **Perennial Allergic Rhinitis** (year-round allergies)
- **Chronic Spontaneous Urticaria** (hives and itching).

How does RUPALL work?

RUPALL is an antihistamine. It blocks the action of histamine and platelet-activating factor (PAF). They are released by the immune system when your body is affected by things you are allergic to. By blocking the action of histamine and PAF, RUPALL helps relieve your allergy symptoms.

What are the ingredients in RUPALL Tablets?

Medicinal ingredients: rupatadine.

Non-medicinal ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised maize starch, red iron oxide and yellow iron oxide.

RUPALL comes in the following dosage forms:

RUPALL Tablets: Each tablet contains 10 mg of rupatadine (as 12.8 mg rupatadine fumarate). Tablets are round and light salmon coloured. Available in blister strips of 3 (sample) and 30 (commercial pack).

Do not use RUPALL Tablets if:

- You or your child are allergic to rupatadine or to any of the other ingredients.
- You or your child have heart problems or a family history of heart problems.
- You or your child take medications called CYP3A4 inhibitors or any other

- medication that may affect the heart rate, such as ketoconazole or erythromycin.
- Your child is younger than 12 years of age. RUPALL Oral Solution is available for use in children 2 to 11 years of age.
 - You or your child have a rare hereditary disease that means you should not eat food containing lactose. The diseases include galactose intolerance, glucose-galactose malabsorption or Lapp lactase deficiency. RUPALL Tablets contain lactose.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RUPALL. Talk about any health conditions or problems you may have, including if you:

- or your child have liver disease.
- or your child have kidney disease.
- or your child have heart problems or a family history of heart problems.
- or your child have low levels of potassium and/or you have a certain abnormal pattern to your heart beat which can occur in some forms of heart disease.
- or your child take medications called CYP3A4 inhibitors or any other medication that may affect the heart rate, such as ketoconazole or erythromycin.

Other warnings you should know about:

Allergic Reactions

Some patients taking RUPALL have experienced:

- sudden and severe allergic reactions, including life-threatening reactions.
- swelling that affects the skin, often around the eyes and lips.
- hives and itching.

Effects on Muscle

Some patients taking RUPALL have experienced muscle weakness or pain.

Pregnancy and Breast-Feeding

It is not recommended to use RUPALL Tablets if you are pregnant or breastfeeding. You should only use the medication if your doctor has told you to.

Lactose Intolerance

RUPALL Tablets contain lactose (a sugar found in milk). If your doctor has said that you or your child cannot have foods with lactose, contact your doctor before taking this medicine.

Elderly Patients

If you are elderly, your doctor may use caution in deciding whether to prescribe you RUPALL Tablets.

Blood Tests

Your doctor may order blood tests for you or your child while you are taking RUPALL Tablets. Rarely, some patients taking RUPALL had:

- an increase in certain blood levels.
- abnormal liver function.

Driving and Using Machines

At the correct dose, RUPALL is not likely to affect driving or use of machines. However, when you or your child first start taking RUPALL, see how the treatment affects either of you before driving or using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RUPALL:

- ketoconazole, itraconazole, voriconazole, posaconazole (used to treat fungal infections)
- erythromycin, azithromycin and clarithromycin (used to treat bacterial infections)
- ritonavir (used to treat HIV/AIDS)
- simvastatin, lovastatin (used to lower cholesterol)
- nefazodone (an anti-depressant)
- diltiazem (used to treat high blood pressure)
- anxiety or sleep medicines that depress the central nervous system
- grapefruit or grapefruit juice (this may increase the level of RUPALL in the body)

At the recommended dose, RUPALL does not increase the drowsiness produced by alcohol.

How to take RUPALL:

Always take RUPALL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Usual dose of RUPALL Tablets:**Adults and adolescents (over 12 years of age):**

One RUPALL Tablet, 10 mg, once daily, with or without food. Swallow tablet whole with a glass of water.

Overdose:

If you think you or your child have taken too much RUPALL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you or your child miss taking a dose of RUPALL Tablets, take it as soon as possible, unless it is almost time for the next dose. Do not take two RUPALL doses at the same time to make up for a missed dose.

What are possible side effects from using RUPALL Tablets?

These are not all the possible side effects you or your child may feel when taking RUPALL Tablets. If you or your child experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- sleepiness
- headache
- dizziness
- dry mouth
- sensation of weakness
- fatigue
- nausea
- pain in the upper or lower abdomen (belly)
- abnormal blood test results (increase in enzyme called creatine phosphokinase)
- symptoms of the common cold and/or flu
- red eyes
- vomiting and diarrhea
- mucus in the back of the nose, throat or sinuses
- throat pain, tonsil pain, pain when swallowing
- cough
- pain during menstruation
- muscle pain and/or muscle weakness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<u>RARE</u> Heart Problems: heart racing or slowing, cold sweats, feeling faint, feeling your heart beat, light headed, nausea, shortness of breath			√
Allergic reaction: symptoms include swelling in the eyes, lips, mouth, tongue, face and throat, itching, rash, hives			√

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect \(http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php\)](http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep RUPALL Tablets in their blister in the outer carton until use in order to protect the product from light. Store at room temperature (15 to 30°C).

Keep out of reach and sight of children.

Do not use RUPALL Tablets after the expiry date which is stated on the carton and blister.

Do not dispose of medicine like RUPALL via wastewater or household waste. Take it to a pharmacy. This will help to protect the environment.

If you want more information about RUPALL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer's website www.medexus.com, or by calling 1-877- 630-5674.

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This leaflet was prepared by Medexus Inc.

Last Revised: January 13, 2023.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

[A1]
PrRUPALL™

**Rupatadine Oral Solution
1 mg/mL rupatadine (as rupatadine fumarate)**

Read this carefully before you start taking **RUPALL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RUPALL**.

What is RUPALL used for?

RUPALL Oral Solution is used in patients 2 to 11 years of age, to treat the symptoms of:

- **Seasonal Allergic Rhinitis** (hay fever)
- **Perennial Allergic Rhinitis** (year-round allergies)
- **Chronic Spontaneous Urticaria** (hives and itching).

How does RUPALL work?

RUPALL is an antihistamine. It blocks the action of histamine and platelet-activating factor (PAF). They are released by the immune system when your body is affected by things you are allergic to. By blocking the action of histamine and PAF, RUPALL helps relieve your allergy symptoms.

What are the ingredients in RUPALL Oral Solution?

Medicinal ingredients: rupatadine.

Non-medicinal ingredients: banana flavor, citric acid anhydrous, disodium phosphate anhydrous methyl parahydroxybenzoate (preservative), propylene glycol, purified water, quinoline yellow, saccharin sodium and sucrose.

RUPALL comes in the following dosage forms:

RUPALL Oral Solution: The solution contains rupatadine 1 mg/mL (as 1.28 mg/mL rupatadine fumarate).

RUPALL Oral Solution is a clear and yellow liquid. It is packaged in an amber-coloured plastic bottle. The bottle has a yellow child-resistant top and a stopper with a hole. Each bottle contains 30 mL (sample) and 120 mL (commercial pack). A plastic syringe with dose markings comes in each carton.

Do not use RUPALL Oral Solution if:

- Your child is allergic to rupatadine or to any of the other ingredients, including the preservative methyl parahydroxybenzoate.
- Your child has heart problems or if there is a family history of heart problems.
- Your child takes medications called CYP3A4 inhibitors or any other medication that may affect the heart rate, such as ketoconazole or erythromycin.
- Your child is not between 2-11 years of age. RUPALL has not been studied in children who are less than 2 years of age. RUPALL should not be given to patients younger than 2 years old. RUPALL Tablets are available for patients 12 years of age and older.
- Your child has a rare hereditary problem that means they should not eat sugar. For example, your child may have fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency. RUPALL Oral Solution contains sucrose.

To help avoid side effects and ensure proper use, talk to your healthcare professional before your child takes RUPALL. Talk about any health conditions or problems your child may have, including if your child:

- has liver disease.
- has kidney disease.
- has heart problems or a family history of heart problems.
- has low levels of potassium and/or a certain abnormal pattern to their heart beat which can occur in some forms of heart disease.
- takes medication(s) called CYP3A4 inhibitors or any other medication that may affect the heart rate, such as ketoconazole or erythromycin.

Other warnings you should know about:**Allergic Reactions**

Some patients taking RUPALL have experienced:

- sudden and severe allergic reactions, including life-threatening reactions.
- swelling that affects the skin, often around the eyes and lips
- hives and itching.

Effects on Muscle

Some patients taking RUPALL have experienced muscle weakness or pain.

Pregnancy and Breast-Feeding

Your child should not use RUPALL Oral Solution if they have gone through puberty and are pregnant or breastfeeding. Your child should only use the medication if their doctor has recommended it.

Sucrose Intolerance

RUPALL Oral Solution contains sucrose (a type of sugar). If your doctor has said that your child cannot have certain sugars, contact your doctor before taking this medicine.

Blood Tests

Your doctor may order blood tests for you or your child while you are taking RUPALL Oral Solution. Rarely, some patients taking RUPALL had:

- an increase in certain blood levels.
- abnormal liver function.

Driving and Using Machines

At the correct dose, RUPALL is not likely to affect driving or use of machines. However, when you first start taking RUPALL, see how the treatment affects your child before riding a bicycle or using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RUPALL:

- ketoconazole, itraconazole, voriconazole, posaconazole (used to treat fungal infections)
- erythromycin, azithromycin and clarithromycin (used to treat bacterial infections)
- ritonavir (used to treat HIV/AIDS)
- simvastatin, lovastatin (used to lower cholesterol)
- nefazodone (an anti-depressant)
- diltiazem (used to treat high blood pressure)
- anxiety or sleep medicines that depress the central nervous system
- grapefruit or grapefruit juice (this may increase the level of RUPALL in your child's body)

At the recommended dose, RUPALL does not increase the drowsiness produced by alcohol.

How to take RUPALL:

Always give your child RUPALL exactly as their doctor has told you. You should check with their doctor or pharmacist if you are not sure.

Usual dose of RUPALL Oral Solution:

Children aged 2 to 11 years with a body weight between 10 and 25 kg:

2.5 mL (2.5 mg) RUPALL Oral Solution, once daily, with or without food.

Children aged 2 to 11 years with a body weight of 25 kg or more:

5 mL (5 mg) RUPALL Oral Solution, once daily, with or without food.

Instructions for Use:

- Open the bottle by pressing the cap and turning it counter-clockwise.
- Take the syringe and put it in the perforated stopper (stopper with a hole) and turn the bottle upside down.

- Fill the syringe with the prescribed dose using the dose markings on the syringe as a guide:
 - Children aged 2 to 11 years with a body weight between 10 and 25 kg:
 - 2.5 mL
 - Children aged 2 to 11 years with a body weight of 25 kg or more:
 - 5 mL
- Administer directly into the mouth from the dosing syringe.
- Wash the syringe after use.

Overdose:

If you think your child has taken too much RUPALL, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If your child missed taking a dose of RUPALL Oral Solution, they should take it as soon as possible, unless it is almost time for the next dose. They should not take two RUPALL doses at the same time to make up for a missed dose.

What are possible side effects from using RUPALL Oral Solution?

These are not all the possible side effects your child may feel when taking RUPALL Oral Solution. If your child experiences any side effects not listed here, contact your child's healthcare professional.

Side effects may include:

- headache
- sleepiness
- dizziness
- dry mouth
- sensation of weakness
- fatigue
- nausea
- pain in the upper or lower abdomen (belly)
- abnormal blood test results (increase in enzyme called creatine phosphokinase)
- symptoms of the common cold and/or flu
- red eyes
- vomiting and diarrhea
- mucus in the back of the nose, throat or sinuses
- throat pain, tonsil pain, pain when swallowing
- cough
- pain during menstruation
- muscle pain and/or muscle weakness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<u>RARE</u> Heart Problems: heart racing or slowing, cold sweats, feeling faint, feeling your heart beat, light headed, nausea, shortness of breath			√
Allergic reaction: symptoms include swelling in the eyes, lips, mouth, tongue, face and throat, itching, rash, hives			√

If your child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your child's healthcare professional.

<p>Reporting Side Effects</p> <p>You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.</p> <p>3 ways to report:</p> <ul style="list-style-type: none"> • Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php); • By calling 1-866-234-2345 (toll-free); • By completing a Consumer Side Effect Reporting Form and sending it by: <ul style="list-style-type: none"> - Fax to 1-866-678-6789 (toll-free), or - Mail to: Canada Vigilance Program Health Canada, Postal Locator 1908C Ottawa, ON K1A 0K9 <p>Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.</p> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>

Storage:

Store RUPALL Oral Solution at room temperature (15 to 30°C).

Keep out of reach and sight of children.

Do not use RUPALL Oral Solution after the expiry date on the bottle and carton.

Do not dispose of medicine like RUPALL via wastewater or household waste. Take it to a pharmacy. This will help to protect the environment.

If you want more information about RUPALL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer's website www.medexus.com, or by calling 1-877- 633-3987.

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This leaflet was prepared by Medexus Inc.

Last Revised: JAN 26, 2023