

Data Sheet

RUPATAL[®]

Rupatadine (as fumarate) 10 mg tablets

Presentation

RUPATAL tablets are round, light salmon pink in colour and with no markings. Each tablet contains 10 mg of rupatadine (as fumarate).

Uses

Actions

Rupatadine is a non-sedating antiallergic compound which displays strong antagonist activity towards both histamine H1 receptors and Platelet-Activating Factor (PAF) receptors. PAF and histamine are known to complement and promote secretion of each other. PAF induces vasodilatation and an increase in vascular permeability, which may be responsible for the appearance of rhinorrhoea and nasal congestion. PAF may have a major role in the late phase allergic reaction. Rupatadine's PAF antagonistic activity represents the likely mechanism behind the inhibition of eosinophil migration which has been suggested to be beneficial in the treatment of chronic urticaria.

In addition, rupatadine is an antiallergic drug with other benefits such as inhibition of mast cell degranulation, neutrophil and eosinophil migration and cytokine release.

Rupatadine shows high H1receptor affinity and little or no activity on other CNS receptors. Rupatadine also has a very long side chain and little liposolubility, therefore, there is little or no crossing of the blood-brain barrier. These properties account for the observed lack of sedation.

Pharmacokinetics

Absorption and bioavailability

Rupatadine is rapidly absorbed after oral administration, with a t_{max} of approximately 0.75 hours after intake. The mean C_{max} was 2.6 ng/mL after a single oral dose of 10 mg and 4.6 ng/mL after a single oral dose of 20 mg. Pharmacokinetics of rupatadine was linear for a dose between 10 and 40 mg. After a dose of 10 mg/day for 7 days, the mean C_{max} was 3.8 ng/mL. The plasma concentration followed a bi-exponential drop-off with a mean

elimination half-life of 5.9 hours. The binding-rate of rupatadine to plasma proteins was 98.5-99 %.

As rupatadine has never been administered to humans by intravenous route, no data is available on its absolute bioavailability.

Effect of food intake

Intake of food increased the systemic exposure (AUC) to rupatadine by about 23%. The exposure to one of its active metabolites and to the main inactive metabolite was practically the same (reduction of about 5% and 3% respectively). The time taken to reach the maximum plasma concentration (t_{max}) of rupatadine was delayed by 1 hour. The maximum plasma concentration (C_{max}) was not affected by food intake. These differences had no clinical significance.

Distribution

Although rupatadine is 98% to 99% bound to human plasma proteins, it is well distributed in other tissues, indicating that this high degree of binding does not cause the compound to be retained in the circulating blood, allowing it to reach its target receptors. Rupatadine displacement from its binding sites when co-administered with other drugs would not be expected, since rupatadine plasma concentrations are far from the level that would exceed plasma binding capacity.

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. Conjugates with glucuronic acid were also found. Some of the metabolites retain antihistaminic activity and may partially contribute to the overall efficacy of the drug and a long duration of the action.

Cytochrome P450 CYP3A4 was identified *in vitro* as the main isoenzyme responsible for the biotransformation of rupatadine and a genetic polymorphism in its biotransformation is unlikely. Other CYP isoenzymes like CYP2C9, CYP2C19 and CYP2D6 are also involved.

Elimination

The plasma concentration followed a bi-exponential drop-off, with a mean elimination half-life of 5.9 hours. In a study of excretion in humans (40 mg of ^{14}C -rupatadine), 34.6% of the radioactive drug administered was recovered in urine and 60.9% in faeces collected over 7 days. Biliary excretion is the most important elimination route for the drug. 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.

Indications

RUPATAL tablets are indicated for symptomatic treatment of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and chronic idiopathic urticaria (CIU) in adults and adolescents (over 12 years of age).

Dosage and Administration

Adults and adolescents (over 12 years of age): The recommended dose is 10 mg/day (one tablet/day), with or without food. Do not halve tablets. Dose equivalence when the tablet is divided has not been established.

Contraindications

Hypersensitivity to rupatadine or to any of the excipients.

Warnings and Precautions

Cardiac safety

Cardiac safety of rupatadine was assessed in a QT/QTc study. Rupatadine at even 10 times the therapeutic dose did not produce any effect on the ECG or have any pro-arrhythmic side effects. 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 and acute myocardial ischemia.

Use in the elderly

Rupatadine 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.

Lower systemic clearance values were observed in elderly volunteers when compared with young volunteers. The mean elimination half-life of rupatadine in elderly subjects is 8.7 hours against 5.9 hours in younger volunteers, perhaps due to a physiological decrease in pre-systemic metabolism. However, since no adverse effects of delayed clearance were noticed and given that the 10 mg dose was well tolerated by elderly volunteers, it is not necessary to make any adjustment when using a dose of 10 mg in the elderly patients.

Use in children

RUPATAL tablets are not recommended for use in children below 12 years of age.

Renal and hepatic impairment

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

Use in pregnancy - Category B2

Data on a limited number of exposed pregnancies indicates no adverse effects of rupatadine on pregnancy or on the health of the foetus/newborn child.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Clinical data for rupatadine or other compounds of the class are inadequate to establish safety in pregnancy. Until such data are available, rupatadine should be used in pregnancy only if the expected benefits clearly outweigh potential risks to mother and foetus.

Use in lactation

Rupatadine is excreted in animal milk. It is unknown whether rupatadine is excreted into breast milk. Due to the lack of human data, rupatadine should be used in breast feeding mothers only if the expected benefits clearly outweigh potential risks to mother and child.

Genotoxicity, Carcinogenicity

Rupatadine was devoid of genotoxic activity in a series of *in vitro* and *in vivo* assays.

In oncogenicity studies in mice over 78 weeks and in rats over 104 weeks, rupatadine showed no direct oncogenic activities. Rupatadine did not increase tumour incidences.

Effects on the ability to drive and use machines

At the recommended dosage, rupatadine is unlikely to affect the ability to drive or use machinery. A few people may be impaired and care should be taken before driving or using machinery until the patient's individual reaction on rupatadine has been established.

At doses higher than 10 mg, cognitive and psychomotor performance may be impaired.

At doses greater than 10 mg there is an unknown effect of rupatadine on driving performance.

Adverse Effects

In clinical studies, rupatadine 10 mg was administered to 2025 patients (120 of whom received rupatadine for at least 1 year) and placebo was administered to 1315 patients.

The most common adverse reactions in controlled clinical studies for rupatadine 10 mg were:

Adverse reaction	Rupatadine 10 mg (%) n = 2025	Placebo (%) n = 1315
Somnolence	9.5	3.4
Headache	6.8	5.6
Fatigue	3.2	2.0

The majority of adverse reactions observed in clinical trials were mild to moderate in severity and usually did not require cessation of therapy. The frequencies are summarised in the following table:

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)
Investigations		Increased blood creatine phosphokinase Increased alanine aminotransferase Increased aspartate aminotransferase Abnormal liver function test
Nervous system disorders	Somnolence Headache Dizziness	Disturbance in attention
Respiratory, thoracic and mediastinal disorders		Epistaxis Nasal dryness Upper respiratory disorders
Gastrointestinal disorders	Dry mouth	Nausea Upper abdominal pain Diarrhoea Dyspepsia Vomiting Abdominal pain Constipation
Skin and subcutaneous tissue disorders		Rash
Musculoskeletal and connective tissue disorders		Back pain Arthralgia Myalgia
Metabolism and nutrition disorders		Increased appetite
General disorders and administration site conditions	Fatigue, Asthenia	Thirst Malaise Pyrexia
Psychiatric disorders		Irritability

POST MARKETING EXPERIENCE

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

Interactions

Interaction with ketoconazole, macrolides or any potential inhibitors of CYP3A4: The concomitant administration of rupatadine 20 mg and

ketoconazole or erythromycin increases the systemic exposure to rupatadine 10 times and 2-3 times respectively. Despite this increase in plasma concentrations of rupatadine, no clinically relevant changes, assessed by ECG parameters, including QTc intervals, laboratory tests and adverse events were observed. However, due to this potential interaction, it is recommended to avoid administration concomitantly with ketoconazole, macrolides or any potential inhibitors of CYP3A4.

Interaction with grapefruit: The concomitant administration of grapefruit juice with rupatadine increased the systemic exposure of rupatadine by 3.5 times. It is recommended to avoid intake of grapefruit juice along with rupatadine.

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 isoenzyme, is unknown. Rupatadine should be used with caution when co-administered with statins.

Interaction with alcohol: When rupatadine is given in combination with alcohol at doses higher than 10 mg, cognitive and psychomotor performance is impaired. Caution should be used when using rupatadine with alcohol.

Overdosage

SYMPTOMS

No case of overdose has been reported. In a clinical safety study, rupatadine at a dose of 100 mg/day for 6 days was well tolerated. The most common adverse reaction was somnolence which was mild and not clinically relevant.

TREATMENT

Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications.

Pharmaceutical Precautions

Shelf life is 36 months from the date of manufacture, stored below 25 °C and protected from light.

Medicine Classification

Prescription Medicine

Package Quantities

Each packet of RUPATAL contains 20 tablets. Sample packs contain 3 tablets.

Further Information

Clinical Trials

The efficacy of rupatadine as a treatment for Allergic Rhinitis (AR) and Chronic Idiopathic Urticaria (CIU) has been investigated in adults and adolescents (over 12 years of age) in several international, randomised, double-blind clinical trials.

These studies demonstrate that rupatadine displays dual activity *in vivo* at doses of 10 mg/day – rupatadine exerts an antihistaminic effect equal to or greater than that of other second generation antihistamines and also displays PAF antagonistic activity.

ALLERGIC RHINITIS (AR)

An exploratory analysis was performed to assess the efficacy of rupatadine, pooling data from ten pivotal clinical studies. Using the seasonal and perennial rhinitis classifications, these studies were re-examined to assess whether the AR characteristics of patients enrolled in these studies met the Allergic Rhinitis and Its Impact on Asthma (ARIA) classification criteria. Intermittent rhinitis was defined when symptoms were present for less than four weeks and persistent when symptoms lasted for more than four weeks.

A total of seven studies were included in this analysis, involving a population of 560 patients with intermittent, and 708 with persistent, allergic rhinitis. Rupatadine 10 mg/day demonstrated significant reduction of Total Symptom Score (Tss) ($p < 0.001$) in comparison with placebo in both intermittent and persistent rhinitis. This study confirms rupatadine 10 mg/day is effective in the control of rhinitis symptoms under the ARIA classification criteria.

Seasonal Allergic Rhinitis (SAR)

Rupatadine 10 mg/day has been shown to be more effective than placebo in alleviating the symptoms of SAR. Rupatadine 10 mg demonstrated better

efficacy ($p < 0.05$) at improving nasal and ocular symptoms of SAR in comparison with placebo over a 14 days treatment period.

The efficacy of rupatadine and cetirizine was compared at 10 mg/day for two weeks in SAR patients. Both groups had similar responses in terms of mean Daily Total Symptom Score (DTSSm) values. However, evaluation of overall efficacy at day 7 revealed that 93.3% patients in the rupatadine group and 83.7% patients in the cetirizine group showed significant improvement ($p = 0.022$). This study suggested a faster effect of rupatadine, since 81.1% of patients on rupatadine had insignificant or absent symptoms of runny nose versus 68.6% in the cetirizine group.

The efficacy of rupatadine at 10 mg was evaluated against loratadine 10 mg over two weeks in SAR patients. Rupatadine was more effective than loratadine at 10 mg/day. Patients on rupatadine demonstrated scores for sneezing and nasal itching which were significantly lower than those observed in patients on loratadine.

The efficacy of rupatadine 10 mg/day was evaluated against placebo on allergen-induced symptoms (including nasal congestion), nasal airflow, nasal secretion and subjective tolerability in response to grass pollen in a controlled allergen exposure chamber. 45 subjects with a history of SAR received rupatadine or placebo every morning for eight days for two subsequent periods which were separated by a 14-day washout interval. On day 8 of each crossover period, subjects underwent a 6-hour allergen exposure in the exposure chamber in which a constant and homogenous concentration of aeroallergens was maintained. The results suggest that, in patients with allergen induced SAR, rupatadine 10 mg/day significantly reduced nasal and non-nasal symptoms as well as nasal secretion and subjective complaints, as compared with placebo. Rupatadine showed a rapid onset of action as indicated by statistically lower total nasal symptom score values compared with placebo, which were observed at the first assessment time during controlled allergen exposure (15 minutes; $p = 0.001$).

Perennial Allergic Rhinitis (PAR)

A study compared rupatadine 10 mg/day, loratadine 10 mg/day, and placebo. Results showed that the percentage of days with score of severe symptoms ≤ 1 (Pd_{max1}) over 28 days' treatment duration for rupatadine (48.7%) and loratadine (48.6%) were consistently better than those for placebo (34.1%). According to DTSSm values, treatments with rupatadine and loratadine were statistically superior to placebo ($p \leq 0.05$). Rupatadine produced a greater reduction in symptom severity compared with placebo in five symptoms, of which rhinorrhoea, sneezing and conjunctival itching were statistically significant ($p \leq 0.05$), whilst differences between loratadine and placebo were statistically significant only for rhinorrhoea and nasal itching ($p \leq 0.05$).

A similar trial was performed comparing rupatadine 10 mg, cetirizine 10 mg and placebo in patients suffering from PAR over a 4 weeks treatment period. Pd_{max1} scores recorded for rupatadine 10 mg and treatment groups were significantly higher than in the placebo group ($p < 0.01$). Patients treated with rupatadine 10 mg and cetirizine 10 mg had lower scores for nasal/non-nasal

symptoms than patients receiving placebo. Investigator and patients reported active treatment to be more effective than placebo at the second and fourth week of therapy.

Recently, a study was conducted to assess the efficacy of rupatadine in moderate to severe PAR. Patients were randomised to treatment with either rupatadine 10 mg, cetirizine 10 mg or placebo once daily for 12 weeks. Rupatadine, but not cetirizine, reduced the baseline Tss statistically more than placebo (47.8% and 38.8%, respectively; p=0.008). Study treatments were well tolerated and no relevant ECG changes or symptomatic lab abnormalities were evidenced throughout the study. Rupatadine maintained its effect over a period of 12 weeks.

CHRONIC IDIOPATHIC URTICARIA (CIU)

The efficacy of rupatadine in patients with CIU was also evaluated in two randomised, double-blind, placebo-controlled clinical trials (total of 617 patients).

The dose finding study was conducted in 283 patients, investigating the effect of treatment with rupatadine (5, 10 or 20 mg, once daily) or placebo over 4 weeks on symptoms and impairment of daily activities and sleep in 12 to 65 year-old patients with moderate to severe CIU. Reductions from baseline in daily mean pruritus score (MPS) over a period of 4 weeks for rupatadine 10 mg/day was 62.0% (p=0.02 versus placebo). Interference with sleep and performance of daily activities also improved with rupatadine 10 mg/day.

The second trial in 334 patients was designed to evaluate the efficacy of rupatadine 10 mg and 20 mg once daily in comparison with placebo for the treatment of CIU symptoms over a four and six week treatment periods. This study confirmed that rupatadine 10 mg/day significantly decreased the MPS from baseline by 57.5% compared with 44.9% with placebo, over the 4-week period.

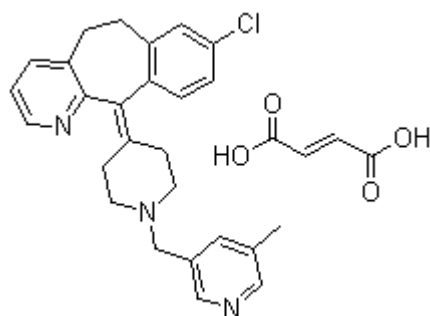
Chemical structure

Chemical names:

CAS name: 8-Chloro-6,11-dihydro-11-[1-[(5-methyl-3-pyridinyl)methyl]-4-piperidinylidene]-5H-benzo[5,6]cyclohepta[1,2-b]pyridine fumarate

IUPAC 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

Chemical structure:



Molecular formulas: $C_{26}H_{26}ClN_3$, $C_4H_4O_4$

Molecular Weight: 532.03

CAS registry no.: 182349-12-8

Excipients

RUPATAL tablets contain the following excipients: pregelatinised maize-starch, microcrystalline cellulose, red iron oxide (E-172), yellow iron oxide (E-172), lactose monohydrate and magnesium stearate.

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® = Registered trademark

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Date of Preparation

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