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Article

# Rupatadine: pharmacological profile and its use in the treatment of allergic rhinitis

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**Abstract:** Rupatadine is a once-daily, non-sedating, selective and long-acting new drug with a strong antagonist activity towards both histamine H1 receptors and platelet-activating factor receptors. The use of rupatadine is indicated in adult and adolescent patients (> 12 years of age) suffering from intermittent and persistent allergic rhinitis. In the treatment of these conditions, rupatadine is at least as effective as ebastine, cetirizine, loratadine and desloratadine. Avery good safety profile of rupatadine has been evidenced in various studies, including a long-term (1-year) safety study. Rupatadine does not present drug–drug interactions with azithromycin, fluoxetine and lorazepam, but should not be administered concomitantly with known CYP3A4 inhibitors.

**Keywords:** antihistamine, platelet-activating factor, rhinitis, rupatadine.

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## Introduction

Allergic rhinitis Allergic rhinitis (AR) has a relevant impact on society because of its high prevalence , association with an impaired quality of life and the presence of comorbidities such as athopy and asthma . Seasonal allergic rhinitis (SAR) is found in ~ 10% of the general population and perennial allergic rhinitis (PAR) in 10 – 20% of the population [1].

SAR is normally triggered by various types of pollens from trees, grasses and weeds, as well as outdoor mould spores. The major symptoms include sneezing, rhinorrhoea, nasal obstruction and nasal or pharyngeal pruritus. Epiphora and itching are also common features [1]. Symptoms of PAR are similar to those of SAR, although nasal obstruction is generally more pronounced. Most patients suffering from PAR are sensitive to one or more nonseasonal allergens, such as moulds or spores, dust mites and animal dander [2]. In both SAR and PAR, the underlying process is an allergic response to airborne allergens of different nature. The disorder is associated with the epithelial accumulation of effector cells, such as mast cells and basophils, and inflammation in the nasal mucosa. Immunological activation of these effector cells induces the secretion of both newly generated (leukotrienes, prostaglandins and kinins) and preformed (histamine and tryptase) proinflammatory mediators [4]. Quantitatively, histamine is the most abundant preformed mediator in the early-phase response and its implication in many of the symptoms of the disease has been clearly demonstrated. Symptoms such as sneezing, itching, watery eyes and rhinorrhoea are largely mediated through histamine H1 receptors [5]. Role of platelet-activating factor in allergic rhinitis Platelet-activating factor (PAF) is an important mediator of AR, as concluded from the effectiveness of the PAF antagonist ABT-491 in rat and guinea-pig models of AR [10, 11]. The biological properties of this mediator include vasodilation and an increase in vascular permeability that may contribute to the appearance of rhinorrhoea and nasal congestion [12, 13]. Both PAF and its metabolite, lyso-PAF, have been detected in the nasal fluids and plasma of patients

with rhinitis [14, 15]. Moreover, PAF and histamine are known to complement each other in vivo; histamine is a mediator of early response, being released from preformed reservoirs in mast cells, whereas PAF is mainly synthesised de novo [16, 17]. Furthermore, each of these mediators is able to promote the release of the other in some tissues and numerous target cells [18]. From the available experimental evidence, it could be reasonable to infer that the blockade of both PAF and histamine receptors could be of superior clinical efficacy than the blockade of only one of these receptor types in the treatment of AR . In considering this, it should be mentioned that although some antihistamines have shown a marginal PAF antagonist properties, these effects can not be attributed to specific interaction with PAF receptors [20, 21].

## Rupatadine

Rupatadine is a novel chemical entity (Figure 1) that shows both antihistamine and anti-PAF effects through its interaction with specific receptors and not through physiological antagonism [22]. This review examines the pharmacological and clinicalprofile of rupatadine and its role in the treatment of allergic disorders. Pharmacokinetic properties Absorption The pharmacokinetic properties of rupatadine administered by the oral route have been studied in healthy volunteers, including elderly subjects of both genders [24]. Rupatadine is rapidly absorbed after oral administration. The Tmax was 0.75 – 1 h (median values).

The Cmax after rupatadine 10 mg in single and repeated doses was 2.2 and 2.0 ng/ml, respectively. The mean t½ in healthy volunteers was ~ 6 h (range 4.3 – 14.3 h). The rapid absorption of rupatadine correlates with the onset of the antihistamine and PAF actions as assessed by wheal and flare inhibition, which occurs within 1 – 2 h post dose. The AUC and Cmax increased in proportion to the dose with a dosage of = 40 mg/day, whereas clearance and t½ remained constant.

## Distribution

Although rupatadine is 98 – 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 coadministered with other drugs would not be expected, as the rupatadine plasma concentrations are far from the level that would exceed plasma binding capacity [23].

## 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 the long duration of action [23]. CYP3A4 was identified in vitro as the main isoenzyme responsible for the biotransformation of rupatadine and a genetic polymorphism in its biotransformation is unlikely [23].

## Excretion

The plasma concentration followed a bi-exponential drop-off, with a mean elimination half-life of 5.9 h. In a study of excretion in humans (14C-rupatadine 40 mg), 34.6% of the radioactivity 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 presystemic metabolism whenadministered orally. The amount of unaltered active substance found in urine and faeces was very low [23].

## Drug interactions and food effect

Metabolic drug–drug interactions of rupatadine were studied after 7 days administration of 20 mg rupatadine plus known CYP3A4 inhibitors, ketoconazole (200 mg/day) or erythromycin (500 mg t.i.d.) [23]. Ketoconazole inhibited both the presystemic and systemic metabolism of rupatadine, increasing the exposure of unchanged drug by approximately tenfold and decreasing the exposure of metabolites. Conversely, ketoconazole kinetics was not affected by rupatadine coadministration. Erythromycin showed lower inhibition of the presystemic metabolism than ketoconazole, leading to a two-to-threefold increase of the systemic exposure to unchanged rupatadine, without significant increases in rupatadine elimination half-life and systemic exposure to the assayed metabolites. Despite this increase in plasma concentrations of the parent compound, no clinically

Indian J Otolaryngol Head Neck Surg
(October-December 2009) 61:320 - 332

relevant changes, assessed by ECG parameters, including QTc intervals, laboratory tests, vital signs and adverse events, were observed. However, due to this potential interaction, it is not recommended to use rupatadine in combination with ketoconazole, macrolides or any potential inhibitors of CYP3A4. A study performed in healthy volunteers evaluated the safety profile of rupatadine when coadministered with azithromycin [25]. Subjects received rupatadine 10 mg/day for 6 days with and without azithromycin. No clinically relevant modifications in mean pharmacokinetic parameters of rupatadine and active metabolites were observed when azithromycin was coadministered. The combination of rupatadine and azithromycin was well tolerated and may be coadministered safely at therapeutic doses with rupatadine 10 mg. Owing to the fact that fluoxetine has been described as a powerful inhibitor of some cytochromes of the P450 family, such as CYP2D6 and CYP3A426, a study was carried out in healthy volunteers to assess the effects of the coadministration of fluoxetine on pharmacokinetic parameters and tolerability of rupatadine [23]. No clinically relevant modifications in mean pharmacokinetic parameters of rupatadine and metabolites were observed when fluoxetine was coadministered. The combination of rupatadine and fluoxetine was well tolerated and fluoxeti safely with rupatadine 10 mg.

A randomised, crossover, double-blind, placebo-controlled clinical trial was performed to evaluate potential changes on mental ability when rupatadine is administered concomitantly with a benzodiazepine. The results demonstrated that rupatadine 10 mg does not impair mental ability and does not potentiate lorazepam-induced mental impairment [23]. A study was performed in healthy volunteers to assess the effects of the coadministration of grapefruit juice on the pharmacokinetic parameters and tolerability of rupatadine and its metabolites. Grapefruit juice showed an inhibition of the presystemic metabolism of rupatadine, increasing the exposure of unchanged drug approximately threefold, without significant increases of systemic exposure of the two metabolites. Based on these results, it is recommended to avoid the intake ofgrapefruit juice when rupatadine treatment is prescribed [23]. Intake of food increased the AUC of rupatadine by ~ 23%. The exposure to metabolites was virtually the same. The Tmax of rupatadine was delayed by 1 h and Cmax was not affected by food intake. These differences had no clinical significance [2].

## Elderly population

Lower systemic clearance (Clss/F) values were observed inelderly volunteers when compared with young volunteers, probably due to a physiological decrease of presystemic metabolism. The mean elimination half-lifes of rupatadine for elderly and young volunteers was 8.7 and 5.9 h, respectively. As rupatadine 10 mg was well tolerated in healthy elderly subjects without clinically relevant adverse events, it was concluded that is not necessary to make any adjustment when using a dose of 10 mg in elderly patients.

## Pharmacodynamic properties

Rupatadine displays strong antagonistic activity towards both histamine H1 and PAF receptors. This activity was demonstrated in studies performed in vitro and in vivo in several animal species, including mice, rats, guinea pigs, rabbits and dogs. In addition, rupatadine has a profile as an anti-allergic drug with potentially beneficial effects, such as the inhibition of mast cell degranulation, inhibition of neutrophil and eosinophil migration and inhibition of cytokine release [27]. The human pharmacodynamic effects of rupatadine, both antihistamine and PAF-antagonist activities, were investigated in terms of its ability to inhibit the flares and wheals produced by intradermal injection of histamine [28,29] and PAF in comparison with placebo and other reference compounds. The specific inhibition of PAF was determined in blood on ex vivo platelet aggregation test induced by PAF. These studies were complemented by a nasal challenge test with a specific allergen in atopic volunteers.

Antihistaminic activity Rupatadine has high affinity for the histamine H1 receptor. The antihistamine activity of rupatadine was compared with that of other first- and second-generation antihistamines using the guinea-pig ileum functional test . It proved to be more active than terfenadine, loratadine, cetirizine, hydroxyzine and diphenhydramine. Some of rupatadine's metabolites also show antihistamine activity in vitro. Rupatadine and desloratadine show similar antihistamine potency in vitro (binding assay Kiapp = 26 and 22 nM; rupatadine and desloratadine, respectively).Low doses of 2 and 5 mg showed inhibition of histamine flares in healthy volunteers of ~ 50%, whereas with placebo inhibition was only 29%. With a 10-mg dose, the percentage of inhibition rose to 60% and lasted until 24 h post dose. In addition,a potent and prolonged inhibitory effect was

demonstrated with 20 mg; a maximum inhibition of 71% was achieved and it remained above 45% until 72 h post dose. Both doses, 10 and 20 mg, showed a significant inhibitory effect on histamine-induced flares in comparison with placebo.

## Platelet-activating factor antagonist activity

The PAF antagonistic action of rupatadine was confirmed by the inhibition of PAF-induced platelet aggregation in rabbit platelet-rich plasma and washed platelets and in dog whole blood, with inhibitory concentration of 50% (IC50) values of 2.9, 0.20 and 0.29 μM, respectively. The in vitro inhibition shown by rupatadine is lower than that of a selective PAF antagonist (WEB-2086). Conversely, the inhibition is much greater than that of the second-generation antihistamines tested, which display little or no PAF antagonist activity. Rupatadine (0.3 – 10 mg/kg p.o.) inhibited the wheal induced by intradermal administration of histamine or PAF in dogs [31], whereas loratadine and cetirizine only inhibited the histamine-induced wheal. The maximum effect of rupatadine occurred after 4 h and significant effects were still observed 24 h after the single-dose administration of the product, indicating a long-lasting effect. Rupatadine also inhibited conjunctivitis in guinea pigs induced by histamine or PAF [32,33]. Loratadine inhibited histamine-induced conjunctivitis, but not that induced by PAF. Moreover, rupatadine applied as an eye lotion was around 10-times more powerful than loratadine against histamine, which concurs with their relative antihistamine activity in vitro .

These studies clearly demonstrate that rupatadine displays dual activity in vivo. Rupatadine shows an antihistamine effect equal to or greater than that of other antihistamines, with the advantage that it is the only compound that also displays PAF antagonist activity.

## Other anti-inflammatory properties

Rupatadine showed potent anti-allergic activity in vitro (mast cell degranulation inhibition, eosinophil chemotaxis) and in vivo in several type I hypersensitivity models. Rupatadine shows a spectrum of activity wider than that of other antihistamines in non-histamine-dependent pharmacological models, such as those involving endotoxin challenge and models of type III hypersensitivity reaction, possibly due to its PAF antagonist properties.

The inhibitory action of rupatadine on mast cell degranulation was investigated, as these effector cells play a fundamental role in allergic processes, mainly in the early-phase response. Rupatadine inhibited mast cell degranulation induced by nonimmunological stimuli (compound 48/80 and calcium ionophore A23187) in rat peritoneal mast cells and also immunological stimuli (Ascaris) in isolated skinmast cells from sensitised dogs [34]. Rupatadine not only inhibited the release of preformed mediators, such as histamine, but also reduced tumour necrosis factor-a release from canine skin mast cells and in the human mast cell line HMC-1 [27,35]. Eosinophils and lymphocytes are key effector cells in the late-phase response of allergy. Rupatadine inhibited eosinophil recruitment in the bronchoalveolar lavage of actively sensitised guinea pigs challenged with antigen [34]. Studies using eosinophils obtained from both nonallergic and allergic volunteers showed that rupatadine (10-9 – 10-7 M) strongly inhibited eotaxin-induced chemotaxis. After in vitro activation of human T cells, rupatadine inhibits the production of inflammatory cytokines. This effect was high for the TH2 cytokine IL-5 [36].

It is generally accepted that most of the anti-inflammatory effect of antihistamine is produced in a histamin receptor-dependent manner; nevertheless, rupatadine, in addition to all antihistamines, has anti-inflammatory effects that act directly on the H1 receptor. In this way, rupatadine has been shown to inhibit the activity of transcription factor AP-1 both dependently and independently from the H1 receptor [37]. Rupatadine has a high H1 receptor binding affinity (Ki 1.6 nM), which allows the molecule to inhibit the histamine-induced IL-6 and IL-8 production using concentrations that are below the plasma levels reached at therapeutic dose [38].

Rupatadine strongly inhibited hypersensitivity reactions in vivo, including both active and passive anaphylaxis in several species [39]. In a model of increased vascular permeability induced by antigen in sensitised beagle dogs, rupatadine displayed strong inhibitory activity [35]. The duration of the anti-allergic effect of rupatadine was prolonged (> 24 h at 1 mg/kg p.o.) and paralleled that observed in studies in which histamine was intradermally injected in dogs [31].

In conclusion, rupatadine shows a very complete anti-allergic and anti-inflammatory profile in various allergy models tested in various species, both in vitro and in vivo, and in healthy and atopic volunteers.

Indian J Otolaryngol Head Neck Surg
(October-December 2009) 61:320 - 332

## CNS and cognitive and psychomotor effects

The effects of rupatadine on the CNS were assessed in several safety pharmacology studies, as well as in other specific tests. Rupatadine did not cause behavioural changes in mice and in cynomolgus monkeys at doses of 100 and 10 mg/kg p.o., respectively. In an ex vivo study in guinea pigs, in which H1 receptor occupancy was assessed in a peripheral tissue (lung) and in the CNS (cerebellum), when rupatadine was administered at doses comparable to those used in humans and effectively blocked the peripheral receptor (therapeutic effect). In contrast, there was almost no blockade of the central receptor. This study revealed a clear dissociation between the effective doses of rupatadine as an antihistamine and those that caused significant blockage of the central receptor. This behavior was similar to that observed with loratadine, a nonsedative antihistamine, but clearly different from that of hydroxyzine, a first-generation antihistamine [41].

A study in healthy volunteers was performed to evaluate the CNS effects of rupatadine (10, 20, 40 and 80 mg) in comparison with a positive standard (hydroxyzine 25 mg), using a randomised, double-blind, crossover, placebo-controlled design [42]. Rupatadine 10 and 20 mg did not produce impairment compared with placebo in objective tests of psychomotor performance and subjective mood scales. A clear CNS impairment was observed only at the highest evaluated doses of 80 mg and with hydroxyzine 25 mg. Rupatadine 10 mg did not seem to reinforce the depressant effect of alcohol (0.8 g/kg) after single dose, both on subjective and objective measurements of psychomotor performance, including quantitative electroencephalography. In addition, a pharmacodynamic interaction was found in the concurrent administration with alcohol when the administered drug was hydroxyzine 25 mg [43]. A study in healthy volunteers was performed to evaluate the effects of rupatadine on driving [44]. All volunteers received a single oral dose of rupatadine 10 mg, hydroxyzine 50 mg or placebo. Driving performance, as evaluated by the Standard Highway Test, Standard Deviation of the Lateral Position, Stanford Sleepiness Scale, Driving Quality Scale and Rate of Sedation, did not show differences between rupatadine and placebo, whereas driving performance was impaired by hydroxyzine.

In conclusion, in the CNS, rupatadine behaves similarly to second-generation antihistamines, generally known as 'non-sedative' antihistamines, but very differently from first-generation antihistamines, such as diphenhydramine and hydroxyzine.

## Anticholinergic effects

Some studies have been conducted to assess the anticholinergic effects of rupatadine, which occur with many of the first-generation antihistamines. No anticholinergic effects were observed in several preclinical models at doses of = 7 mg/kg (> 40-times the human expected dose) [23]. Rupatadine did not show peripheral anticholinergic activity at single doses in the range of 10 – 80 mg in humans [30].

## Clinical studies

The efficacy of rupatadine as a treatment for AR has been investigated in adults and adolescents (aged = 12 years) in several international, randomised, double-blind and multi-centre trials.

The target study population were patients suffering from moderate-to-severe AR. As it was intended to recruit patients in the acute stage of the disease, patients had to score > 5 points for nasal symptoms in a standardised scale at inclusion. This ensured that only patients suffering from an acute episode of at least mild intensity would be included. A history of AR of at least 2 years before inclusion was required and documented by clinical records.

The main efficacy variables in these studies were based on the daily subjective assessment of the symptom severity recorded by the patients in their diaries. Mean daily total symptom score (DTSSm; main variable in SAR studies) corresponded to the mean of the daily symptom scores recorded for each of the assessed symptoms [45]. The percentage of days with score of severe symptoms = 1 (Pdmax1; main variable inPAR studies) corresponded to the percentage of days during the study period in which, for each patient, the score of the most severe symptom on each day was < 1 [46]. Mean daily symptom score (DSSm) was a secondary variable that allows the assessment of the mean score for a given symptom; this is the mean of all the scores recorded for a given symptom per patient and for all the study days. Overall efficacy impression was calculated from the score assigned by both the investigator and the patient in all studies, according to conventional scale.

## Seasonal allergic rhinitis

Dose-ranging, placebo-controlled studies to evaluate the efficacy and safety of several doses of rupatadine showed that all doses of rupatadine were more effective than placebo in alleviating the symptoms in a dose-dependent manner [47]. A summary of the clinical trials covering the indications of SAR is provided in Table 1. Rupatadine 10 and 20 mg were clearly superior ($p < 0.05$) for improving nasal and ocular symptoms of SAR in comparison with placebo [48]. No significant differences were detected between rupatadine 10 and 20 mg. However, a general trend towards a quicker relief of symptoms with rupatadine 20 mg after the week 1 of treatment was detected.

Guadaño et al. [49] compared rupatadine 10 mg and ebastine 10 mg to placebo once daily for 2 weeks in SAR patients. Significant differences were detected in DTSSm between rupatadine treatment and placebo (33% lower for rupatadine group; $p = 0.005$) after 2 weeks of treatment. Total symptom scores were 22% lower for rupatadine than for ebastine, although differences were not statistically significant. Regarding the symptom-by-symptom analysis of scores, rupatadine had the optimum scores with a notable degree of superiority over ebastine and placebo. Rupatadine produced a greater reduction in the severity of all symptoms evaluated compared with placebo and these differences were statistically significant in sneezing, rhinorrhoea, tearing and nasal itching. The greatest difference between active treatments and placebo was for runny nose (rupatadine versus placebo, $p = 0.001$; ebastine versus placebo, $p = 0.005$).

Martínez-Cócera et al. [50] investigated the efficacy rupatadine 10 mg or cetirizine 10 mg/day for 2 weeks in adults with SAR. Rupatadine 10 mg and cetirizine 10 mg elicited similar response evaluated by means of DTSSm values. In the investigator's global evaluation of efficacy on day 7, 93.3 and 83.7% patients in the rupatadine and cetirizine groups, respectively, showed a significant improvement ($p = 0.022$). Running nose at day 7 of treatment was absent or not significant in 81.1% of patients in the rupatadine group and in 68.6% of patients in the cetirizine group ($p = 0.029$), thus suggesting a faster effect of rupatadine.

In the study of Saint-Martin et al. [51], the efficacy of rupatadine 10 and 20 mg versus loratadine 10 mg was examined over 2 weeks in SAR patients. Rupatadine at both doses was more effective than loratadine 10 mg; patients treated with rupatadine 10 and 20 mg demonstrated scores for sneezing and nasal itching that were significantly lower than those of patients treated with loratadine 10 mg.

In a second trial, which compared rupatadine 10 and 20 mg versus loratadine 10 mg, the study demonstrated that during a 2-week period, all three treatment groups were very similar, with no statistically significant differences. However, symptom scores were numerically better with rupatadine 20 mg than with the two other treatments, sometimes reaching statistical significance [47].

A recent trial was performed to evaluate the efficacy of rupatadine 10 mg/day and 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 (Vienna Challenge Chamber [VCC]) [52]. In a randomised, double-blind, placebo- controlled, crossover trial, 45 subjects with a history of SAR received rupatadine or placebo every morning for 8 days for two subsequent periods, which were separated by a 14-day wash-out interval. On day 8 of each crossover period, subjects underwent a 6-h allergen exposure in the VCC, in which a constant and homogeneous concentration of aeroallergens was maintained. Subjective and objective assessments were performed online during the exposure. Subjective single and composite nasal and non-nasal symptoms were consistently less severe with rupatadine than placebo, starting from the assessment time up to 15 min before end of the 6-h VCC challenge, with the most significant effects seen for nasal rhinorrhoea, nasal itching, sneezing attacks and total nasal symptoms (all $p < 0.0001$). All other symptoms (including nasal congestion, $p = 0.005$) were also significantly reduced with the active treatment compared with placebo. These findings indicated that, in subjects with allergen-induced SAR, rupatadine significantly reduced the severity of all SAR-related nasal (including nasal congestion) and non-nasal symptoms, as well as nasal secretion and subjective overall feeling of complaint, 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 already at the first assessment time during VCC exposure (15 min; $p = 0.001$).

## Perennial allergic rhinitis

Several studies have also been performed in order to evaluate the efficacy and safety of rupatadine compared with placebo

Indian J Otolaryngol Head Neck Surg
(October-December 2009) 61:320 - 332

**Table 1.** Summary efficacy of rupatadine in adults and adolescents (aged > 12 years) with seasonal allergic rhinitis.

| Ref. | Study design | RU dose & comparative treatment | Treatment duration | Number of patients (randomised/treated) | Efficacy results(DTSSm) |
|---|---|---|---|---|---|
| 47 | R, DB, PC | 10mg/20mg | 2 weeks | 178/174 | RU 10Vs PL* / RU 20 Vs PL* |
| 48 | R, DB, PC | 5 mg/10 mg/20 mg | 2 weeks | 395/392 | RU 5 vs PL‡ / RU 10 vs PL*<br>RU 20 vs PL§ |
| 49 | R, DB, PC | 10 mg / EBA(10 mg) | 2weeks | 250/243 | RU 10 vs PL‡ / EBA vs PL ns |
| 50 | R, DB | 10 mg / 20 mg<br>CTZ(10mg) | 2 weeks | 373/362 | RU 10 vs CTZns<br>RU 20 vs CTZns |
| 51 | R,DB | 10 mg / 20 mg<br>LOR(10mg) | 2 weeks | 339/339 | RU 10 vs LOR ns /<br>RU 20 vs LOR* |
| 48 | R, DB | 10 mg / 20 mg<br>LOR(10mg) | 2 weeks | 332/331 | RU 10 vs LOR ns<br>RU 20 vs LOR ns |
| 52 | R, DB, PC | 10 mg / DES (5mg) | 4 weeks | 379/359 | RU 10 vs PL‡ / DES vs PL‡ |

CTZ: Cetirizine; DB: Double-blind; DES: Desloratadine; DTSSm: Daily total symptom score (mean); EB: Ebastine; LOR: Loratadine; ns: Not significant; PC:

Placebo-controlled; PL: Placebo; R: Randomised; RU: Rupatadine.

*p = 0.05. ‡p = 0.01. §p = 0.001.

**Table 2.** Summary efficacy of rupatadine in adults and adolescents (aged > 12 years) with perennial allergic rhinitis.

| Ref. | Study design | RU dose & comparative treatment | Treatment duration | Number of patients (randomised/treated) | Efficacy results (Pdmax1 or DTSSm) |
|---|---|---|---|---|---|
| 48 | R, DB, PC | 10 mg / 20 mg | 4 weeks | 248/ 245 | RU 10 vs PL* / RU 20 vs PL* |
| 48 | R, DB, PC | 10 mg / 20 mg<br>LOR(10 mg) | 4 weeks | 283/283 | RU10vsPL* / RU20vs PL*<br>LOR vs PL* |
| 48 | R, DB, PC | 10 mg / EBA(10 mg) | 4 weeks | 223/ 219 | RU10vs PL* / EBA vs PL* |
| 48 | R, DB, PC | 10 mg / 20 mg<br>CTZ (10 mg) | 4 weeks | 282/ 273 | RU10vs PL‡ / RU20vs PL§<br>CTZ vs PL‡ |
| 54 | R, DB, PC | 10 mg / CTZ (10 mg) | 12 weeks | 543/ 542 | RU10vs PL* CTZvsPL ns |

CTZ: Cetirizine; DB: Double-blind; DES: Desloratadine; DTSSm: Daily total symptoms score (mean); EB: Ebastine; LOR: Loratadine; ns: Not significant; Pdmax1: % days with score of severe symptoms = 1; PC: Placebo-controlled; PL: Placebo; R: Randomised; RU: Rupatadine.

*p = 0.05. ‡p = 0.01. §p = 0.001.

or other antihistamines in the treatment of PAR. These studies are summarized in Table 2.

A dose-ranging, placebo-controlled study demonstrated that rupatadine 10 and 20 mg provided better efficacy than placebo; however, a dose relationship was not established in this trial [47].

A study comparing two dosage levels of rupatadine (10 and 20 mg), loratadine 10 mg and placebo was performed [47]. Results indicated that, during the 28-day treatment period, mean Pdmax1 values for rupatadine and loratadine were consistently better than for placebo (34.1%). The superior mean Pdmax1 value recorded was for rupatadine 20 mg (50.4 %) and was slightly lower for rupatadine 10 mg (48.7 %) and loratadine 10 mg (48.6 %). Statistically significant differences for mean Pdmax1 were only detected between rupatadine 20 mg and placebo. According to DTSSm values, the two active treatments with rupatadine and loratadine were superior to placebo, reaching statistical significance in all three active treatment groups.

Rupatadine produced a greater reduction in symptom severity than placebo in the five symptoms considered, of which rhinorrhoea, sneezing and conjunctival itching were statistically significant. Differences between loratadine andplacebo were statistically significant only for runny nose and itchy nose. The symptom of runny nose was significantly improved for both rupatadine dose levels and loratadine than with placebo. Patients' overall impression indicated that both doses of rupatadine were superior to placebo.

Another study comparing rupatadine 10 mg, ebastine 10 mg and placebo was performed to evaluate the efficacy and safety rupatadine in controlling PAR symptoms after 28 days . Pdmax1 for the two active treatment groups (rupatadine and ebastine) was consistently better than for placebo. Both active treatments demonstrated similar Pdmax1 values and the inferior value was observed with placebo. Regarding the analysis of individual symptom scores, the two active treatments showed statistically significant reductions of scores compared with placebo. Rupatadine 10 mg produced a greater reduction in symptom severity than placebo in all the five symptoms considered and these differences were statistically significant for sneezing, itchy nose and itchy eyes. Differences between ebastine and placebo were statistically significant only for symptoms of sneezing and itchy nose. Patients' overall impression of efficacy indicated that both rupatadine and ebastine were more effective than placebo. Furthermore, the investigator overall impression indicated that only rupatadineshowed statistical significance over placebo.

A similar trial was performed comparing two dosage levels of rupatadine (10 and 20 mg), cetirizine 10 mg and placebo was also performed in patients suffering from PAR [47]. Pdmax1, scores recorded in all three active treatment groups were statistically significantly more effective than the placebo group ($p < 0.0001$). The best value was reported with rupatadine 20 mg in comparison with placebo ($p < 0.0001$). Rupatadine 10 mg and cetirizine 10 mg (43%) improvements were both also superior to placebo ($p < 0.01$). There were no significant differences in the pairwise comparison between the three active treatment groups.

Patients treated with rupatadine 10 and 20 mg, as well as with cetirizine 10 mg, had lower scores for evaluated symptoms than placebo. Individual symptom scores for active treatments were better than with placebo ($p < 0.001$). Differences reached higher levels of significance in all four nasal symptoms (including nasal obstruction) and neared significance ($p = 0.057$) in conjunctive itching. Finally, investigator rating of overall efficacy was similar to that of patients. Both reported active treatments to be more effective than placebo at the second and last week of therapy.

Recently, a new study was concluded to assess the efficacy the rupatadine in moderate-to-severe persistent AR [53]. Patients were randomised to treatment with either rupatadine 10 mg, cetirizine 10 mg or placebo once daily during 12 weeks. The primary efficacy endpoint was the 12-week average change from baseline of the patients' total symptom score (TSS).

Rupatadine, but not cetirizine, reduced the baseline TSS statistically more than placebo ($p = 0.008$). The onset of action in the change from baseline of the TSS was at day 2 (rupatadine 10 mg versus placebo; $p = 0.013$). Study treatments were well tolerated and no relevant ECG findings or symptomatic laboratory abnormalities were evidenced throughout the study.

## Safety

### Global safety

A total of 3490 patients or healthy volunteers have been exposed to rupatadine in clinical studies. The adverse effects found in 2025 subjects exposed to rupatadine 10 mg in clinical trials are summarised in Table 3.

Indian J Otolaryngol Head Neck Surg
(October-December 2009) 61:320 - 332

It should be mentioned that 120 patients were exposed during 12 months in one long-term safety clinical study in patients with persistent AR [57]. The aim of this study was the evaluation of the long-term safety of rupatadine according to the recommendations of the European Medicines Agency guidelines [58,59]. The more frequent treatment-related AE during this period were somnolence (6%) and headache, dry mouth, fatigue and rash, which were reported with an incidence < 1%. No relevant ECG findings or symptomatic laboratory abnormalities were evidenced throughout the study.

This study confirmed the good long-term safety profile of rupatadine, which is the first compound that has evidenced a good safety profile after 1 year of treatment.

**Cardiac safety**

A prolonged QTc interval on the ECG is a feature that has been associated with drug-induced torsades de pointes (TdP), a potentially fatal polymorphic ventricular tachycardia identified by the continuously twisting appearance of the QRS complex in the 12-lead ECG. In recent years, there had been concern about the cardiotoxicity of nonsedative antihistamines with reports of TdP, first with astemizole and later with terfenadine. The initial belief that the cardiotoxicity was a class effect of non-sedating antihistamines proved unfounded, since fexofenadine, the active metabolite that mediates the antihistamine actions of terfenadine, does not seem to have these cardiotoxic effects. In accordance with the recommendations of the Guideline ICH E14, June 2004 [61], a 'thorough QT/QTc study' [62] was performed in order to determine if rupatadine has a threshold pharmacological effect on cardiac repolarisation, as detected by QT/QTc interval prolongation. The validity of the trial was demonstrated by the fact that moxifloxacin, the positive. control group, demonstrated the expected change in QTc duration. The ECG data for rupatadine at both 10 and 100 mg showed no signal of any effects on the ECG. There was no gender effect, pharmacodynamic-kinetic relationship of rupatadine and its main metabolites or imbalance in outliers, which also confirmed the lack of any signal of rupatadine,especially on QTc duration. This study demonstrated that rupatadine, at = 10-times the therapeutic dose, does not have any proarrhythmic side effect.

Therapeutic and clinical use The approved dose of rupatadine is 10 mg/day. It has been demonstrated that rupatadine at this dose is at least as effective as ebastine, loratadine, cetirizine and desloratadine in the treatment of AR and better than placebo. Rupatadine has a good safety profile and is devoid of arrhythmogenic potential.

## Conclusion

Rupatadine is a once-daily, nonsedative, selective and long-acting H1 antihistamine with antagonistic PAF effects though its interaction with specific receptors. In the treatment of AR, rupatadine 10 and 20 mg/day is better than placebo and at least as effective as ebastine, cetirizine, loratadine and desloratadine, with a possible faster effect than cetirizine. In comparison with placebo, rupatadine significantly improves nasal symptoms in patients with AR.

A good safety profile of rupatadine has been evidenced in randomised clinical trials. Adverse events related to rupatadine have been similar to those with comparators. However, two aspects concerning safety deserve comment: firstly, there is available evidence that comes from a study specifically designed to evaluate safety, which shows that rupatadine is safe when administered over 1 year; and secondly, evidence from a 'thorough QT/QTc study' shows that rupatadine at doses of 10 – 100 mg/day (10-times the approved dose) is devoid of any proarrhythmic effect. Moreover, as deduced from an ad hoc study, rupatadine does not affect driving performance. Rupatadine does not present drug–drug interactions with azithromycin, fluoxetine and lorazepam and these drugs can therefore be administered in patients who are concomitantly treated with these drugs. Rupatadine should not be administered concomitantly with erythromycin, ketoconazole or grapefruit. Rupatadine is an effective and safe second-generation antihistamine in the treatment of AR. Table 3. Summary of incidence of related adverse drug reactions in comparison with placebo in clinical controlled studies.

| Related adverse events | Treatment Rupatadine 10 mg (n = 2025)n % | Placebo (n = 1315) n % |
|---|---|---|
| Headache | 139 6.8 | 74 5.6 |
| Somnolence | 192 9.5 | 45 3.4 |
| Dizziness | 21 1.0 | – – |
| Fatigue | 64 3.2 | 26 2.0 |
| Asthenia | 30 1.5 | – – |
| Dry mouth | 24 1.2 | – – |

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