

Review Article

Rupatadine in allergic rhinitis and chronic urticaria

Histamine is the primary mediator involved in the pathophysiology of allergic rhinitis and chronic urticaria, and this explains the prominent role that histamine H₁-receptor antagonists have in the treatment of these disorders. However, histamine is clearly not the only mediator involved in the inflammatory cascade. There is an emerging view that drugs which can inhibit a broader range of inflammatory processes may prove to be more effective in providing symptomatic relief in both allergic rhinitis and chronic urticaria. This is an important consideration of the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative which provides a scientific basis for defining what are the desirable properties of an 'ideal' antihistamine. In this review of rupatadine, a newer dual inhibitor of histamine H₁- and PAF-receptors, we evaluate the evidence for a mechanism of action which includes anti-inflammatory effects in addition to a powerful inhibition of H₁- and PAF-receptors. We assess this in relation to the clinical efficacy (particularly the speed of onset of action) and safety of rupatadine, and importantly its longer term utility in everyday life. In clinical trials, rupatadine has been shown to be an effective and well-tolerated treatment for allergic rhinitis and chronic idiopathic urticaria (CIU). It has a fast onset of action, producing rapid symptomatic relief, and it also has an extended duration of clinical activity which allows once-daily administration. In comparative clinical trials rupatadine was shown to be at least as effective as drugs such as loratadine, cetirizine, desloratadine and ebastine in reducing allergic symptoms in adult/adolescent patients with seasonal, perennial or persistent allergic rhinitis. Importantly, rupatadine demonstrated no adverse cardiovascular effects in preclinical or extensive clinical testing, nor negative significant effects on cognition or psychomotor performance (including a practical driving study). It improved the overall well-being of patients with allergic rhinitis or CIU based on findings from quality of life questionnaires and patient global rating scores in clinical trials. Thus, rupatadine is a recently introduced dual inhibitor of histamine H₁- and PAF-receptors, which has been shown to be an effective and generally well-tolerated treatment for allergic rhinitis and chronic urticaria. It possesses a broader profile of anti-inflammatory properties inhibiting both inflammatory cells and a range of mediators involved in the early- and late-phase inflammatory response, but the clinical relevance of these effects remain to be clarified.

**J. Mullol¹, J. Bousquet², C. Bachert³,
W. G. Canonica⁴, A. Gimenez-Arnau⁵,
M. L. Kowalski⁶, E. Martí-Guadano⁷,
M. Maurer⁸, C. Picado⁹, G.
Scadding¹⁰, P. Van Cauwenberge³**

¹Unitat de Rinologia, Servei d'ORL, Hospital Clinic, IDIBAPS, Barcelona, Spain; ²University Hospital, Montpellier and INSERM, France; ³Department of Oto-rhino-laryngology, Gent University Hospital, Gent, Belgium; ⁴Allergy & Respiratory Diseases, DIMI, Department of Internal Medicine, University of Genoa, Genoa, Italy; ⁵Dermatology Department, Hospital del Mar, Barcelona, Spain; ⁶Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Lodz, Poland; ⁷Servei d'Al·lèrgia, Fundació Hospital Sant Pere Claver, Barcelona, Spain; ⁸Department of Dermatology and Allergy, Allergie Centrum-Charité/ECARF, Charité – Universitätsmedizin Berlin, Germany; ⁹University of Barcelona, Servei de Pneumologia i Al·lèrgia Respiratoria, Hospital Clinic, Barcelona, Spain; ¹⁰Royal National Throat, Nose and Ear Hospital, London, UK

Key words: allergic rhinitis; antiallergic antihistamines; chronic urticaria; H₁-receptor antagonists; PAF-receptor antagonists; rupatadine.

J. Mullol
Unitat de Rinologia
Servei d'ORL
Hospital Clinic
IDIBAPS
Barcelona
Spain

All authors of this article are members of the Rupatadine Advisory Board for Grupo Uriach S.A.

Accepted for publication 14 December 2007

The increasing prevalence of allergic diseases is becoming a major healthcare concern and it remains largely unexplained (1–3). Potential causes include the 'hygiene hypothesis', which speculates that reduced exposure to

allergens during childhood increases the risk of allergy (4), or the 'pollution hypothesis', which suggests that changes in allergen-distribution patterns and/or individual responses to specific allergens (including new aller-

gens) may be responsible and this is exacerbated by atmospheric pollution (3). Another theory implicates a major shift in the gene pool, predisposing more individuals to excessive immunoglobulin E (IgE) production, and therefore increased expression of many atopic diseases such as allergic rhinitis, atopic dermatitis and asthma (2). However, the latter theory appears unlikely given the short period during which prevalence rates have increased (3). The American Academy of Allergy Asthma and Immunology (AAAAI) estimate that more than 50 million US Americans suffer an allergic disease each year – this represents about 20% of the USA population. The range of allergic diseases includes rhinitis, sinusitis, asthma, dermatitis and food allergy, and all of these disorders negatively impact the patient's quality of life (QoL). This impairs their ability to perform in school or the workplace and thus results in significant socio-economic costs (5, 6).

The role of histamine in the pathophysiology of allergic disorders is well-established. Therefore, it is not surprising to find that agents, which block the effects of histamine (antihistamines), play a pivotal role in the treatment of such diseases (1, 2, 7–12). However, as discussed later in this review, numerous other mediators are implicated in the inflammatory cascade, which plays such a central role in the response to allergen challenge. In this review of rupatadine, a recently introduced dual antagonist of histamine H₁- and platelet-activating factor (PAF)-receptors, the main focus relates to its clinical usefulness in allergic rhinitis and chronic urticaria, two disorders for which antihistamines remain a first-line treatment option.

Allergic rhinitis

Allergic rhinitis is a major IgE-mediated chronic respiratory disorder, which has traditionally been subdivided, based on time of exposure, into seasonal and perennial disease. Seasonal allergic rhinitis (SAR) is usually caused by a wide variety of outdoor allergens such as pollen and moulds while perennial allergic rhinitis (PAR) is most frequently caused by indoor allergens, such as dust mites, animal dander, insects and moulds. This subdivision is not ideal as there are many examples which fall outside of the 'norm'. For example, there are places where pollens and moulds are perennial allergens (e.g. grass pollen allergy in parts of the USA) and some symptoms of perennial disease are not always present all year round (1). In 2001, the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop group, in collaboration with the WHO, introduced a new classification system for allergic rhinitis based on the duration of symptoms and their severity (1, 8, 9).

- 1 Intermittent allergic rhinitis: symptoms are present for <4 days a week or for <4 weeks.
- 2 Persistent allergic rhinitis (PER): symptoms are present for >4 days a week and for >4 consecutive weeks.

3 Mild: all of the following items should be present: normal sleep; no impairment of daily activities, sport or leisure; no impairment of work or school; and no troublesome symptoms.

4 Moderate to severe: one or more of the following events should occur: abnormal sleep; impairment of daily activities, sport or leisure; impaired work or school; or troublesome symptoms.

This new classification recognizes allergic rhinitis as a significant chronic respiratory disease with important co-morbidities, including asthma, for which allergic rhinitis is a risk factor (1). It also supports a stepwise approach to therapy in which second-generation antihistamines such as rupatadine are an important component (9).

The fact that we now have two systems of classification does pose certain problems with regards the 'integrity' of the clinical literature when investigating the overall clinical efficacy and tolerability/safety of antihistamines. In this review, we have made it very clear as to which classification system has been employed when evaluating clinical trials involving rupatadine in patients with allergic rhinitis.

Allergic rhinitis is a global health problem and it is one of the top 10 reasons for patients visiting their general practitioner (13). Furthermore, many patients self-treat and do not visit their physician. In Europe, the prevalence of clinically confirmable allergic rhinitis was estimated to range from 17% (Italy) to 29% (Belgium) with a mean value of 23% across the six countries involved in the study (14). Interestingly, in this study population, 45% of subjects were previously undiagnosed and the highest rate of nondiagnosis was in patients with perennial rhinitis. In the United States, allergic rhinitis is the most common atopic disease and it has been estimated that it affects up to 25% of adults and >40% of children at some stage (15). Staggeringly, 80 million individuals experience symptoms of allergic rhinitis for >7 days/year and the socio-economic costs are significant as the disorder impacts QoL, school performance, socialization and work performance/productivity (15, 16). In terms of the type of allergic rhinitis, it has been estimated that SAR occurs in about 10% of the general population whilst PAR occurs in about 10–20% (17).

The AAAAI estimate that as many as 3.8 million days per year are lost from school or work in the US as a result of allergic rhinitis. Furthermore, it is now recognized that a number of co-morbid conditions are associated with allergic rhinitis including asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection (RTI), and dental occlusion. The cost of treating these conditions needs to be considered when assessing the overall socio-economic impact of the disease (18). Asthma and rhinitis are linked by physiological, pathological and epidemiological characteristics and their co-morbid link has led to the concept of 'one airway, one disease' (19).

Chronic urticaria

Chronic urticaria is a common often debilitating disease, which is characterized by daily, or almost daily, experience of wheals, erythemas, and pruritus. It is often accompanied by angio-oedema and persists for six or more weeks. Besides being bothersome and debilitating, the public nature of the skin disorder can be stressful and often results in sleep disturbances, disruption of daily activities and ultimately, fatigue/loss of energy. The QoL of the patient is then severely impaired (20).

Historically, the aetiology of the disease has often been poorly defined, which led to it being termed chronic idiopathic urticaria (CIU) in many cases. However, various different causes of chronic urticaria have been identified (e.g. chronic bacterial infections, intolerance to food constituents, autoimmune processes, etc.) and they have been shown to result in the generation of mast cell-activating signals that lead to the activation and degranulation of skin mast cell populations (11, 12, 21). This has led to recent attempts to rationalize the nomenclature and classification of urticarial diseases based on factors such as aetiology and chronicity (11, 22, 23). In this review the term 'chronic urticaria' is used while discussing the disease in general. It should be noted, however, that clinical trials with rupatadine have only included patients with CIU, which would come under the subheading of 'spontaneous urticaria' in accordance with the recent European Academy of Allergology and Clinical Immunology (EAACI) recommendations (22, 23).

Chronic idiopathic urticaria has been reported to occur in 0.1–3% of the populations of Europe and the US, and it has been estimated that its worldwide lifelong prevalence is approximately 0.5% and does not vary significantly within different populations (21, 24). The disorder often has a variable course with spontaneous remissions and relapses over periods of several years (25). H₁-receptor antagonists are widely used as first-line treatment in chronic urticaria, but a customized approach is required, given the high variability of the disease and this often requires higher than recommended dosages, combination therapy and/or occasionally immunomodulatory therapy (11).

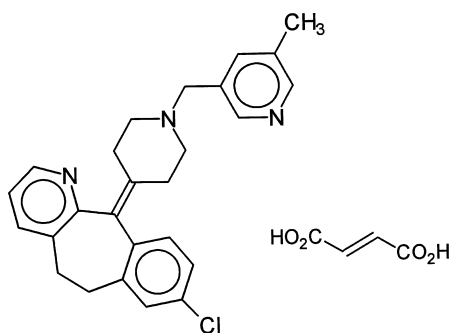


Figure 1. Structural formula of rupatadine.

Rupatadine: overview

Rupatadine, an *N*-alkyl pyridine derivative (Fig. 1), is classified as a new second-generation antihistamine and it possesses both peripheral H₁- and PAF-receptor antagonist properties. It is administered orally once daily and is advocated for the treatment of histamine-related (inflammatory) disorders such as allergic rhinitis and chronic urticaria.

Much of the early data concerning the pharmacology (mechanism of action, and the pharmacokinetic and pharmacodynamic properties) of rupatadine have been reviewed elsewhere (26–30) and are briefly summarized in Table 1. Systematic review of the clinical efficacy and safety of rupatadine has highlighted its broad range of activity and confirmed its excellent tolerability when used in the management of allergic rhinitis and chronic urticaria. The aims of this review are to augment these earlier articles with more recent clinical findings, and to address some specific issues raised by the 'ARIA' and 'Consensus Group on New Generation Antihistamines (CONGA)' initiatives in relation to determination of the desirable properties for an 'ideal' antihistamine (1, 2, 8, 9). In this regard three specific questions will be addressed:

- 1 What is the evidence for a mechanism of action, which includes anti-inflammatory effects in addition to a powerful inhibition of H₁- and PAF-receptors?
- 2 What is the evidence supporting the potency and clinical efficacy of rupatadine, and what data are available regarding the speed of onset of action of this newer antihistamine?
- 3 Finally, what aspects of the pharmacological and clinical activity of rupatadine impact on its long-term utility in everyday life? In particular, what data are

Table 1. Overview of the pharmacological profile of rupatadine (28, 29, 47)

Parameter	Pharmacological profile	
	Single dose	Multiple once daily doses
Mechanism of action	Histamine H ₁ -receptor antagonist; PAF-receptor antagonist; other anti-inflammatory activity	
Pharmacokinetics	Single dose	Multiple once daily doses
<i>C</i> _{max} (ng/ml)	2.3	1.9
<i>t</i> _{max} (h)	0.8	0.75–1.0
AUC _{0–24} (ng/ml/h)	7.6	8.4
<i>C</i> _{max} /AUC	Increases in <i>C</i> _{max} and AUC were linear with single doses of 10–40 mg	
Effect of food intake	Minimal with a slight increase in <i>t</i> _{max}	
Protein binding	High: 98–99%	
Metabolism	Extensive presystemic hepatic metabolism via oxidative processes and glucuronide conjugation. CYP3A4 is primarily responsible for rupatadine metabolism. Some metabolites are active (e.g. desloratadine and its hydroxylate derivative)	
Elimination <i>t</i> _{1/2} (h)	4.6	5.8
Elimination	60.9% in feces and 34.6% in urine	
Effect of age	Increased <i>C</i> _{max} and AUC and decreased clearance were of little clinical relevance	

available concerning its tolerability/safety, possible drug–drug interactions, cardiotoxicity and central nervous system (CNS) effects and how do these properties influence patient well-being and QoL?

What is the evidence for a mechanism of action which includes anti-inflammatory/anti-allergic effects in addition to a powerful inhibition of H₁- and PAF-receptors?

Background

Allergic rhinitis is a complex and multifactorial IgE-mediated immunological disorder, which is associated with the epithelial accumulation of effector cells such as mast cells, eosinophils and basophils as well as the formation and release of a variety of different inflammatory mediators. The accumulated inflammatory cells are in an activated state and the mediators released by these cells are responsible for the early symptoms of rhinitis such as nasal itch, sneezing and rhinorrhoea (31). Pathophysiologically, the disease is characterized as a two-phase process involving an initial sensitization phase (allergen exposure resulting in IgE over-expression and binding to receptors on mast cells and basophils) with subsequent allergen exposure provoking an allergic response. Clinically the allergic response can be divided into two phases:

- 1 The early-phase (immediate) inflammatory response, which is initiated within minutes of re-exposure to the allergen and is primarily caused by mast cell degranulation and the release of preformed mediators such as histamine and proteases, and newly generated mediators such as cysteinyl leukotrienes (LT), cytokines [various interleukins (IL-4, 5 and 6), bradykinin, tumour necrosis factor (TNF- α)], chemotactic factors, PAF, and granulocyte macrophage-colony stimulating factor (GM-CSF). For the patient, the most obvious effect of these mediators is to produce the early symptoms of allergic rhinitis such as sneezing, itching, and rhinorrhoea. In addition, they stimulate the production, adhesion and infiltration into local tissue of circulating inflammatory cells such as eosinophils, basophils, monocytes, and lymphocytes (31, 32).
- 2 The late-phase inflammatory response begins 2–4 h after allergen exposure and, generally speaking, involves the activated inflammatory cells which release further mediators, promoting local edema and tissue damage, and continuation of the overall inflammatory process. Symptomatically, the late-phase allergic reaction is characterized by nasal congestion and obstruction (32).

A schematic representation of the allergic inflammatory cascade is shown in Fig. 2 and it highlights the wide range of cells and mediators that have been identified as

contributing to the co-ordinated complex immunological response to allergen exposure in the clinical expression of allergic rhinitis (31–35).

Urticaria is characterized by the rapid appearance of wheals and/or angio-oedema and can present in a variety of forms (11, 22, 23). A wide range of eliciting stimuli have been implicated in the pathogenesis of urticaria including physical factors, drugs, foodstuffs, infectious agents, cold, autoimmunity, etc. However, many cases remain idiopathic despite intensive investigation (23). In spite of the fact that urticaria can present in a great diversity of forms, its treatment follows a systematic approach involving avoidance of the eliciting stimulus, inhibition of mast cell-mediator release or treatment of the target tissues for mast cell mediators (11).

The role of histamine as a prominent mediator in the pathophysiology of allergic rhinitis and urticaria is unequivocal, and this explains the primary role that histamine H₁-receptor antagonists have had, both historically and in current best practice guidelines in these disease settings. However, histamine is clearly not the only mediator involved in the inflammatory process and there is an emerging view that drugs which can inhibit a broader range of inflammatory agents may prove to be more effective in providing symptomatic relief in both allergic rhinitis and chronic urticaria (31, 36).

In this section of the review, we will assess the activity of rupatadine, a newer dual inhibitor of histamine H₁- and PAF-receptors, on a range of mediators that have been implicated in allergic rhinitis and chronic urticaria.

Antihistaminic activity

Binding studies. Rupatadine possesses high affinity for histamine H₁-receptors and in this regard it has been compared with a number of first- and second-generation antihistamines in various binding-assay studies. For example, in guinea pig cerebellum membranes rupatadine was as potent as loratadine and terfenadine in displacing ³H-mepyramine from its binding site on H₁-receptors; the apparent dissociation constant K_i for the three antihistamines were 102, 127, and 144 nM, respectively (37). In the same model, rupatadine was shown to more vigorously displace ³H-mepyramine from H₁-receptors than either loratadine or fexofenadine as determined by the drug concentration required to inhibit the displacement by 50% (IC₅₀) which were 26, 196, and 267 nM, respectively. In a human cell line (human umbilical vascular endothelial cells; HUVEC) rupatadine displayed the highest H₁-receptor-binding affinity as assessed by the inhibition of mepyramine-binding. In Chinese hamster ovary (CHO) cells, the apparent dissociation constant K_i was 1.4 nM for rupatadine compared with 1.6 nM for desloratadine, 9.5 nM for levocetirizine, and 40.3 nM for fexofenadine (38).

Allergic reaction

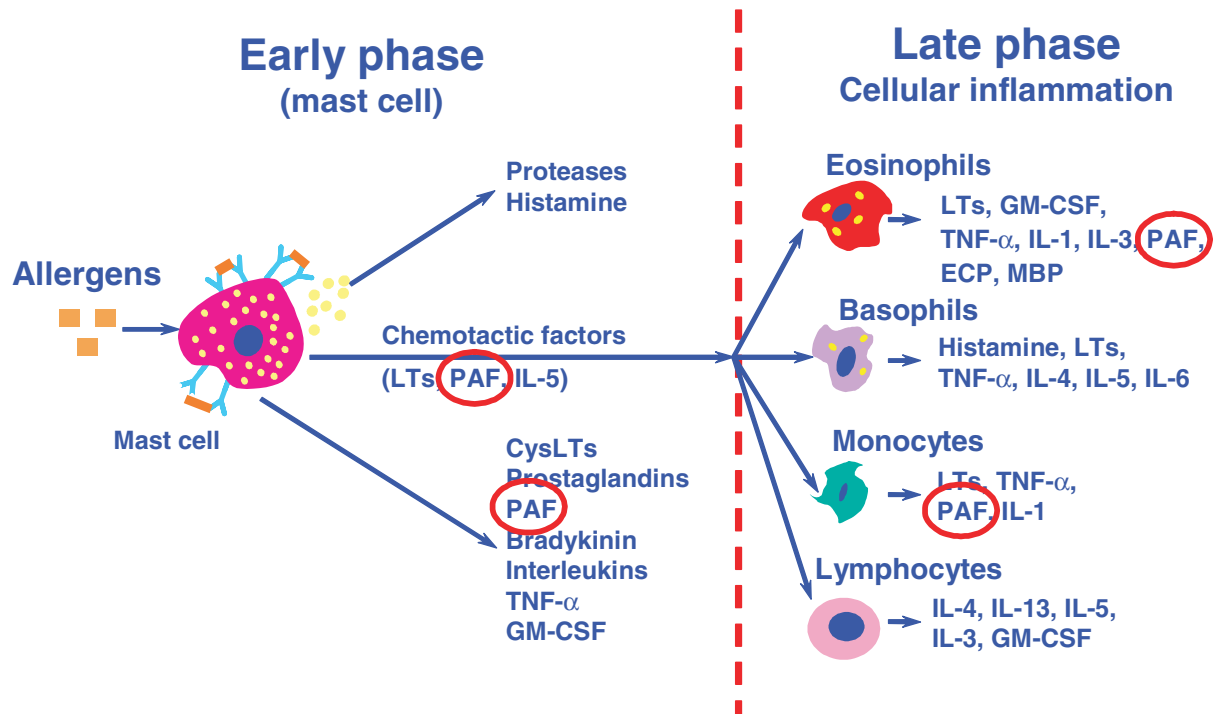


Figure 2. Schematic representation of the allergic inflammatory cascade (adapted from references 32–35).

Rupatadine demonstrated a marked selectivity for binding to peripheral lung H_1 -receptors compared with brain (cerebellum) H_1 -receptors following oral administration of 0.16 mg/kg to guinea pigs. As assessed by *ex vivo* 3H -mepyramine binding, receptor occupancy was 70% for lung and <10% for cerebellum receptors (39). Similar findings were reported for loratadine, whereas hydroxyzine showed no differentiation between lung and brain (30% and 50% occupancy, respectively) and diphenhydramine only weakly blocked the lung receptor (<10%).

In vitro experiments, and studies in animals and humans. Rupatadine displayed potent antihistaminic activity *in vitro*, and in animal and human studies (27, 28, 37, 39–46). For example, Merlos et al. (37) compared the effectiveness of a range of antihistamines with respect to inhibiting histamine-induced contractions in guinea pig ileum. Rupatadine behaved as a competitive antagonist in this model and it was shown to be 24 times more potent than cetirizine, 75 times more potent than loratadine and 95 times more potent than terfenadine (Table 2). In other *in vitro* models of antihistaminic activity the following findings were documented for rupatadine:

Table 2. The concentration of various antihistamines to produce 50% inhibition (IC_{50}) of histamine-induced contractions in guinea pig ileum (37)

Antihistamine	Mean IC_{50} nM (95% CL)	Relative potency ^a
Rupatadine	3.8 (3.1–4.6)	1
Chlorpheniramine	6.1 (4.6–8.0)	1.6
Ketotifen	21 (12–38)	5.5
Cetirizine	90 (58–140)	23.7
Clemastine	231 (136–391)	60.8
Hydroxyzine	276 (199–382)	72.6
Loratadine	286 (170–480)	75.3
Diphenhydramine	321 (212–485)	84.5
Terfenadine	362 (258–508)	95.3

^aConcentration required to produce an equivalent effect to rupatadine.

- 1 Rupatadine was almost four times more potent than loratadine (IC_{50} 5.3 μ M vs 19 μ M) in inhibiting antigen (*Ascaris suum*)-induced histamine release in isolated canine skin mast cells (43).
- 2 Rupatadine and loratadine were similarly effective in inhibiting histamine release provoked by A23187, concanavalin A and anti-IgE, in isolated canine skin

mast cells (40), and in inhibiting A23187-induced histamine release from rat peritoneal mast cells both *in vitro* and *ex vivo* (37).

- 3 The selectivity of rupatadine for histamine H₁-receptors was confirmed by its lack of effect on acetylcholine-, serotonin-, or LTD₄-induced contractions of guinea pig ileum *in vitro* (37).

The antihistaminic activity of rupatadine has been evaluated in a variety of animal models with the following results:

- 1 Rupatadine was 15-times more potent than loratadine (IC₅₀ 0.11 mg/kg vs 1.6 mg/kg) in inhibiting histamine-induced bronchospasm in guinea pigs (37). It was also 3.4 times more potent than loratadine against histamine-induced hypotension in normotensive rats (IC₅₀ 1.4 mg/kg vs 4.7 mg/kg) (37).
- 2 In antigen (*Ascaris suum*)-induced skin inflammation in dogs, both rupatadine and loratadine, administered orally, inhibited wheal formation in a dose-dependent manner. At the lowest dosage (0.1 mg/kg), the effects of rupatadine lasted significantly longer than those of loratadine, and at the highest dosage (10 mg/kg) rupatadine produced significantly greater inhibition of wheals (84% vs 64%; *P* < 0.05) (43).
- 3 Rupatadine, cetirizine, levocabastine, and loratadine at dosages of 1 or 10 mg/kg displayed similar maximum potencies (75–85% wheal inhibition) 4–8 h after oral administration (42).
- 4 Like other antihistamines such as levocabastine and loratadine, rupatadine was effective against histamine- and ovalbumin-induced conjunctivitis in guinea pigs (41, 45). In this model, rupatadine was found to be 20-fold more potent than loratadine (IC₅₀ values at 30 min were 0.0015% and 0.034%, respectively) (45).

In patients with allergic rhinitis, rupatadine rapidly and significantly reduced nasal and non-nasal symptoms compared with placebo following allergen exposure in the Vienna Challenge Chamber (see sections Seasonal allergic rhinitis and Fast onset of action of rupatadine) (46). Izquierdo et al. (47) determined the effects of single doses of rupatadine 10, 20, and 40 mg as well as multiple doses 20 or 40 mg once daily for 7 days on histamine-induced cutaneous flares in healthy male volunteers. Both the percentage and duration of flare inhibition increased with dosage reaching maximum values of 69%, 82%, and 93% after the 10, 20 and 40 mg doses. After multiple doses, the inhibition of cutaneous flares increased rapidly and remained high (70–90%) throughout the study. These findings have more recently been replicated in a crossover study involving 18 healthy volunteers who received single doses of rupatadine 10, 20, 40, and 80 mg, hydroxyzine 25 mg or placebo (48). In this study, rupatadine 80 mg and hydroxyzine 25 mg produced similar levels of wheal inhibition.

Platelet-activating factor antagonist activity

Platelet-activating factor is an endogenous phospholipid inflammatory mediator produced by inflammatory cells such as alveolar macrophages, eosinophils, mast cells, basophils, platelets, and neutrophils in response to allergic/inflammatory stimuli (49). It has been implicated in a wide range of biological responses and pathological conditions, and most pertinent to this review is its association with increased vascular permeability, eosinophil chemo-attraction, bronchoconstriction, airways hyper-responsiveness and their involvement in the pathophysiology of rhinitis and asthma. In addition, PAF is detectable in inflammatory skin such as lesions associated with urticaria and psoriasis, but it is not present in normal skin, and intradermal injection of the phospholipid induces a wheal and flare reaction typical of urticaria (50).

Binding studies. In radioligand receptor-binding studies, rupatadine displaced the potent and selective PAF antagonist WEB-2086 from its binding site on rabbit platelet membranes with a K_i value of 550 nM. In this model it was 25 times less potent than SCH-37370 (a dual PAF- and histamine-receptor antagonist) and 2.5 times less potent than the specific PAF-receptor antagonist ginkgolide-B (37).

In vitro experiments and studies in animals and humans. Rupatadine demonstrated competitive PAF-antagonistic activity in the submicromolar range *in vitro*, with IC₅₀ values of 0.2 and 0.68 μM in models, which assessed platelet aggregation in washed rabbit platelets and human platelet-rich plasma, respectively (37). In these models, the anti-PAF activity of rupatadine was lower than that of the specific PAF antagonists WEB-2086 and ginkgolide-B, but significantly greater than that of antihistamines such as loratadine, ketotifen, mepyramine and terfenadine (Table 3). Likewise, rupatadine (IC₅₀ 4.6 μM) was significantly more potent than loratadine (IC₅₀ 142 μM), cetirizine (IC₅₀ > 200 μM), and fexofenadine (IC₅₀ > 200 μM) against PAF-induced platelet aggregation in platelet-rich rabbit plasma. Rupatadine was a specific inhibitor of PAF as it did not antagonize platelet aggregation induced by ADP or arachidonic acid at concentrations up to 100 μM (37).

The PAF-antagonist activity of rupatadine has been evaluated in a variety of animal models with the following results:

- 1 Rupatadine was more than 30-times more potent than loratadine (IC₅₀ 0.0096 mg/kg vs > 0.3 mg/kg) in inhibiting PAF-induced bronchospasm in guinea pigs (37) and it was also more than 10-times more potent than loratadine against PAF-induced hypotension in normotensive rats (IC₅₀ 0.44 mg/kg vs > 5 mg/kg) (37).

Table 3. The concentration of various antihistamines/PAF antagonists to produce 50% inhibition (IC₅₀) of PAF-induced antagonism of platelet aggregation in washed rabbit platelets and human platelet-rich plasma (37)

Antihistamine	Washed rabbit platelets		Human platelet-rich plasma	
	Mean IC ₅₀ μM (95% CL)	Relative potency ^a	Mean IC ₅₀ μM (95% CL)	Relative potency ^a
WEB-2086	0.017 (0.014–0.021)	0.085	0.11 (0.1–0.12)	0.16
SCH-37370	0.025 (0.016–0.039)	0.125	0.33 (0.28–0.4)	0.49
Ginkgolide-B	0.037 (0.024–0.037)	0.185	Not tested	Not tested
Rupatadine	0.20 (0.17–0.24)	1	0.68 (0.5–0.92)	1
Loratadine	32 (24–43)	160	>200	>290
Ketotifen	>100	>500	Not tested	Not tested
Mepyramine	>100	>500	Not tested	Not tested
Terfenadine	>100	>500	Not tested	Not tested

^aConcentration required to produce an equivalent effect to rupatadine.

- Rupatadine displayed dose-dependent activity against PAF-induced wheal formation in dogs, and the effects were significantly greater than those observed for other antihistamines such as cetirizine, levocabastine, and loratadine (40). In this model peak effects with rupatadine were noted after 4 h and the effects lasted 12–48 h depending on the dose administered.
- Rupatadine was effective against PAF-induced conjunctivitis in guinea pigs. In this model neither loratadine nor levocabastine demonstrated any significant PAF antagonistic activity (39, 41).
- Rupatadine protected against PAF-induced mortality in mice and in this model it was approximately one-third as potent as WEB-2086, whereas loratadine was ineffective (35).

The activity of rupatadine in relieving PAF-induced cutaneous flares was confirmed in a dose-ranging study in healthy volunteers (28). In this cross-over clinical study the following dose-related effects were observed:

- Rupatadine 10 mg significantly reduced flare area by a maximum of 41% at 24 h.
- Rupatadine 20 mg reduced flare area by 42% at 6 h and this rose to a maximum of 56% at 24 h and the effect was maintained for up to 48 h;
- Rupatadine 40 mg reduced flare area by 68% at 4 h and this rose to a maximum of 87% at 6 h and the effect was remained above 60% until 72-h postadministration.
- Rupatadine 80 mg reduced flare area by 91% at 4 h and this rose to a maximum of 93% at 48 h and the effect was still evident 96 h after administration.

The same group showed that single oral doses of rupatadine 40 and 80 mg significantly inhibited *ex vivo* PAF-induced platelet aggregation in healthy volunteers. The inhibition of platelet aggregation commenced within 2 h and reached a maximum at 4 h, and no significant anti-PAF effects were observed at 24-h postadministration (28).

Other anti-inflammatory/anti-allergic effects of rupatadine

The development of ‘anti-allergic’ antihistamines, i.e. drugs which not only block histamine H₁-pathways, but also modify mast cell degranulation, inhibit inflammatory cell recruitment, and/or block LT production would be expected to provide greater benefit in terms of improving symptomatic relief (31). The studies described above confirm the activity of rupatadine on histamine H₁-receptors and show that unlike many other first- and second-generation antihistamines, it produces specific and competitive inhibition of PAF-receptors. Furthermore, its anti-allergic/anti-inflammatory activity extends beyond these classical pathways as evidenced by its activity in *in vitro* models such as inhibition of mast cell degranulation and eosinophil chemotaxis, as well as its activity in *in vivo* type 1 hypersensitivity models. The broader spectrum of the anti-allergic activity of rupatadine on inflammatory cell lines and chemical mediators will be reviewed in this section.

Effect on mast cells. As noted earlier, mast cell degranulation plays a fundamental role in the early-phase allergic reaction and it is also well accepted that this can lead to a late phase reaction in which mast cells and other inflammatory cell components are key contributors. Rupatadine has been shown to inhibit mast cell degranulation induced by both immunological and non-immunological stimuli in isolated skin mast cells from sensitized dogs (28, 42–44). In this model the effects of rupatadine were comparable to those of loratadine (Fig. 3). Both drugs inhibited the release of histamine in a concentration-dependent manner with no statistically significant differences between them, although rupatadine tended to produce a greater overall effect. Other studies have shown that rupatadine not only inhibited the release of preformed mediators such as histamine, it also reduced the release of LTC₄ from rat peritoneal mast cells, and TNF-α from canine skin mast cells and from a human mast cell line. It is thought that these properties may have

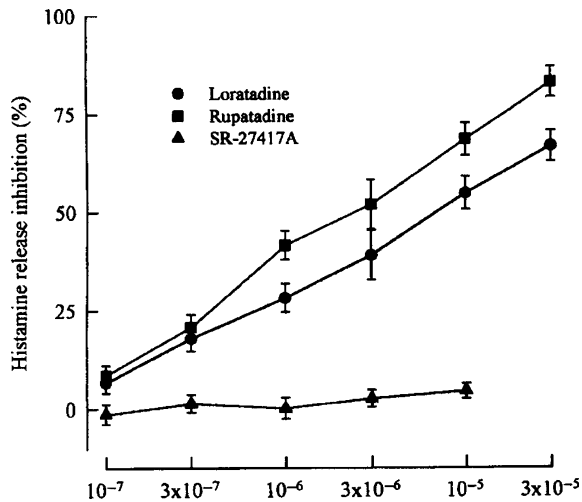


Figure 3. Mean percentage inhibition of antigen (*Ascaris Suum*)-induced histamine release from canine skin mast cells by repatadine, loratadine and the PAF antagonist SR-27417A. (From Queralt et al 1998 (43). Reprinted with permission of John Wiley & Sons, Inc.).

a beneficial effect on the late-phase allergic reaction (40, 44, 51).

Effect on eosinophils and neutrophils. In rhinitis, the recruitment of eosinophils, neutrophils, and other effector cells, as part of the late-phase response of the allergic reaction, appears to underlie the clinical expression of the disease. A number of studies have assessed the impact of rupatadine on aspects of inflammatory cell function in various models of the inflammatory process.

Barrón et al. (52) showed that rupatadine at concentrations of 10–100 nM inhibited human eosinophil chemotaxis induced by eotaxin and this effect occurred

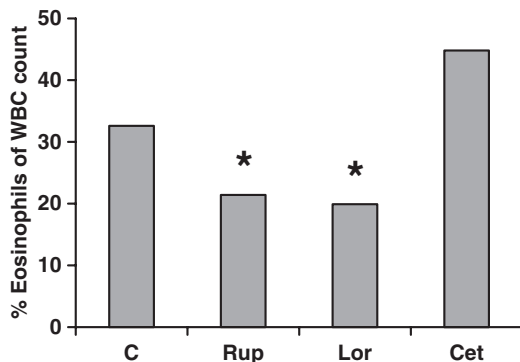


Figure 4. Percentage eosinophils of white blood cell (WBC) count in bronchoalveolar lavage (BAL) frotis obtained from ovalbumin-sensitized guinea pigs following rechallenge with allergen and pretreatment with vehicle alone (C), rupatadine (Rup), loratadine (Lor) or cetirizine (Cet). **P* < 0.05 vs control. (Adapted from Merlos et al. 1998; 53).

independent of whether the eosinophils were obtained from healthy volunteers or eosinophilic donors. Rupatadine was also observed to inhibit the recruitment of eosinophils in the bronchoalveolar lavage of actively sensitized guinea pigs challenged with ovalbumin (53) In this model rupatadine and loratadine were equally effective and both were more effective than cetirizine (Fig. 4).

Rupatadine inhibited human neutrophil chemotaxis induced by PAF and LTB₄. When PAF 10 nM was the induction agent, the inhibitory effects of rupatadine were dose-dependent (47). In this model rupatadine had a greater effect than other antihistamines such as cetirizine, fexofenadine, loratadine, and mizolastine (54).

Effect on cytokine production. The inhibitory effects on pro-inflammatory cytokine production (IL-6 and IL-8) of a range of antihistamines (rupatadine, desloratadine, levocetirizine, and fexofenadine) were determined in HUVEC cells activated by histamine (55). IC₅₀ values were lowest for rupatadine followed by desloratadine, levocetirizine, and fexofenadine (Table 4). There appeared to be a direct relationship between binding to the H₁-receptor (as determined by the apparent dissociation constant *K_i* value) and the capacity of the antihistamines to inhibit pro-inflammatory mediator release in this model. Similar results were reported in a comparison of rupatadine and desloratadine (52). IC₅₀ values of 9 and 5 pM for inhibition of IL-8 and IL-6 expression were recorded for rupatadine, with much higher concentrations required for desloratadine (110 and 180 pM, respectively).

Rupatadine was also found to inhibit the production of a range of lymphocyte cytokines (IL-5, IL-6, IL-8, GM-CSF and TNF-α) using two different methods of activation; firstly with anti-CD3/anti-CD28/IL-2 and secondly with anti-CD3/VCAM (vascular cell adhesion molecule) (56). Desloratadine produced a similar pattern of cytokine inhibition for GM-CSF and IL-8. However, rupatadine was significantly (*P* < 0.01) more effective than desloratadine at inhibiting the release of TNF-α, IL-5, and IL-6 from human lymphocytes when administered simultaneously with cell activation, and at inhibiting the release of IL-5 from activated cells when the drugs were administered prior to activation. The differential effect for

Table 4. Concentration of various antihistamines to inhibit interleukin (IL)-6 and IL-8 production by 50% (IC₅₀) in human umbilical vascular cells (HUVEC) activated by histamine (38)

Antihistamine	Mean IC ₅₀ (nM)	
	IL-6	IL-8
Rupatadine	0.046	0.040
Desloratadine	0.1	0.12
Levocetirizine	2.2	2.4
Fexofenadine	21	Not achievable

rupatadine over desloratadine is unlikely to be a general effect on T cells as the degree of inhibition varied according to the tested cytokine. Furthermore, the more pronounced effect of rupatadine against the T-helper 2 (Th2) cytokine IL-5 may confer advantages in the treatment of allergic inflammation.

Effects on adhesion molecules and transcription factors. Rupatadine produced a dose-dependent inhibition of neutrophil adhesion molecule expression (CD18 and CD11b) following stimulation with PAF (49). The effect was more pronounced for CD11b (~75% inhibition with rupatadine 10 µM) than for CD18 (~20% inhibition with rupatadine 10 µM).

It is generally accepted that most of the anti-inflammatory effects of antihistamines are produced via histamine H₁-receptor dependent pathways although additional anti-allergic and anti-inflammatory effects are well documented in the literature (8, 31, 57). The role played by the H₁-receptor in relation to the additional effects of antihistamines remains controversial and an action on transcription factors such as NF-κB and AP-1 cannot be ruled out (58). Indeed, rupatadine was reported to inhibit NF-κB activity induced by histamine in a HUVEC cell line and it also inhibited an increase in NF-κB activity induced by an over-expression of histamine H₁-receptors in a CHO cell line. These effects were paralleled by reductions in IL-6 and IL-8 production which are both regulated by NF-κB (Table 4; 55).

In a study involving human alveolar epithelial cells rupatadine inhibited NF-κB and AP-1 activities induced by histamine via its H₁-receptor, and in this regard it was similar to other antihistamines such as desloratadine and levocetirizine. In this model, rupatadine and desloratadine, but not levocetirizine, were able to inhibit NF-κB activity independently from histamine and the H₁-receptor, but only rupatadine was able to inhibit AP-1 activity independently from H₁-receptor pathways (58).

Conclusions

- 1 Various pharmacological studies have confirmed that rupatadine is a powerful selective antagonist of the histamine H₁-receptor which, unlike other antihistamines such as loratadine and levocetirizine, also produces specific and dose-dependent inhibition of PAF receptors.
- 2 Indeed, rupatadine was found to be a competitive inhibitor of PAF receptors at submicromolar concentrations and this corresponded with dose-dependent activity in animal models such as PAF-induced wheal formation in dogs.
- 3 Augmenting these classic anti-inflammatory properties, rupatadine has also been shown to inhibit other potential inflammatory processes/mediators such as mast cell degranulation (provoked by both immuno-

logical and nonimmunological stimuli), eosinophil and neutrophil chemotaxis, cytokine (IL-5, IL-6, IL-8, GM-CSF, and TNF-α) production and neutrophil adhesion molecule (CD11b and CD18) expression.

- 4 Based on these findings rupatadine is an antihistamine, which possesses a broader profile of anti-inflammatory effects; inhibiting both inflammatory cells and a range of mediators involved in the early- and late-phase inflammatory responses.
- 5 It has been suggested that antihistamines with a wider range of anti-inflammatory/anti-allergic properties will provide better symptomatic relief in disorders such as allergic rhinitis and chronic urticaria.
- 6 It will be interesting to see if the pharmacological/immunological evidence reported for rupatadine translates into long-term clinical benefits in patients.

What is the evidence supporting the potency and clinical efficacy of rupatadine, and what data are available regarding the speed of onset of action of this newer antihistamine?

Background

The efficacy of once-daily oral rupatadine in the management of allergic rhinitis and chronic urticaria in adolescents and adults (aged ≥12–65 years) has been evaluated in a broad range of well-controlled clinical trials including:

- 1 Dose-ranging studies (2.5–20 mg once daily).
- 2 Placebo-controlled studies.
- 3 Comparative studies with other antihistamines.

All of the trials were appropriately designed to reduce errors that may be caused by variation or bias (they were randomized, double-blind, parallel group, multicentre comparisons and usually included a placebo group), with the exception of the open clinical trial of Mion et al. (59). Based on standards applied to the evaluation of the validity and quality of clinical data (see Appendix) the majority of trials with rupatadine represent well controlled level 2 evidence.

The patient populations were generally well-defined and appropriate for the scientific/medical question being addressed and the following characteristics were required:

- 1 Only adult and adolescent patients aged ≥12–65 years were included.
- 2 SAR: ≥2-year history of moderate-to-severe SAR caused by pollens PAR: ≥2-year history of moderate-to-severe PAR caused by an allergen CIU: clinical manifestations of urticaria for at least 6 weeks
- 3 For SAR/PAR/chronic urticaria, all patients were required to be suffering an acute attack (SAR/PAR; a score of ≥5 for nasal symptoms; CIU a score of ≥2, which is indicative of moderate pruritus).

- 4 For SAR/PAR a positive skin prick test at study entry or within the previous 12 months, and/or a positive radioallergosorbent test.

The majority of clinical trials involving patients with allergic rhinitis used the older classification system, which categorized patients as suffering from SAR or PAR based on the season of exposure. However, a small number of studies/analyses have been published which classified patients according the newer ARIA criteria (1, 8, 9) for intermittent and persistent rhinitis and these will be discussed separately. In addition, a number of trials have been published assessing the efficacy and tolerability of rupatadine in patients with CIU. Again, these used the more traditional classification system based upon the idiopathic nature of chronic urticaria, whereas using current EAACI recommendations, they would be categorized under the sub-grouping of 'spontaneous urticaria'.

Much of this clinical data has been reviewed elsewhere (28–30) and these systematic reviews have highlighted the broad range of activity of rupatadine and confirmed its efficacy and excellent tolerability when used in the management of allergic disorders. In this section, we will augment earlier findings with more recently published clinical data on allergic rhinitis and chronic urticaria, and we will address a specific clinical question related to the rapidity of the onset of action of rupatadine. The time to symptom relief is an important consideration for patients, in terms of improving their general well-being and QoL, enabling them to return to normal daily routines/work.

Seasonal allergic rhinitis

Clinical studies with rupatadine in patients with moderate-to-severe SAR are summarized in Table 5. In a series of dose-ranging, placebo-controlled trials rupatadine 2.5–20 mg once daily was clearly more effective than placebo in alleviating nasal and ocular symptoms of SAR in a dose-dependent manner (28, 60, 61). Overall, however, the 10 and 20 mg dosages were the most effective and there was little to choose between them in terms of symptom relief and patient/investigator global ratings. This was confirmed in a pooled analysis involving 1368 patients with moderate-to-severe SAR who were treated with rupatadine 2.5–20 mg once daily (61). The main finding of this study confirmed the efficacy of rupatadine in reducing mean daily total symptom scores (mDTSS), and covariate analysis found no age- or sex-related differences.

Based on a balance of symptom relief, patient and investigator preference, and tolerability/safety, rupatadine 10 mg once daily was chosen as the preferred option and this is now the recommended adult starting-dosage. However, it should be noted that there was a trend towards faster symptom relief with rupatadine 20 mg

after 1-week treatment (29) and this point will be discussed in more detail in the section, Fast onset of action of rupatadine.

In well-controlled comparative studies involving other antihistamines, rupatadine was shown to be at least as effective as drugs such as cetirizine, ebastine, loratadine, and desloratadine in relieving nasal and ocular symptoms in patients with SAR (Table 5). Overall, the various antihistamines produced similar high levels of symptomatic relief in SAR, although the following differences were observed:

- 1 In a per-protocol analysis rupatadine 10 and 20 mg once daily were significantly more effective than loratadine 10 mg once daily in improving mDTSS ($P = 0.03$; Fig. 5) and a number of secondary efficacy variables such as the maximum daily symptom score (DSS_{max}), investigator clinical symptom scores (CSS) for sneezing and nasal itching, and change in total CSS from baseline to day 14 (62).
- 2 After 7 days' treatment both investigator global assessment ($P = 0.02$) and absence of running nose ($P = 0.03$) were significantly better with rupatadine 10 mg once daily than with cetirizine 10 mg once daily. This is indicative of a faster onset of action with rupatadine (63).
- 3 Rupatadine 10 mg once daily significantly reduced mDTSS compared with placebo whereas the improvement produced by ebastine 10 mg once daily did not reach statistical significance. Furthermore, rupatadine improved four symptoms of SAR compared with placebo whereas ebastine only improved two individual symptoms (64).

Two well-designed (randomized, double-blind, placebo-controlled, crossover) clinical trials in patients with SAR employed objective measures for assessing changes in disease severity/symptomatology during treatment with rupatadine. Valero et al. (65) used acoustic rhinometry to measure airways obstruction following nasal allergen challenge in 30 patients with SAR. At 2-h postchallenge nasal volume was reduced 18.6% in the placebo group vs 9.8% in the group that had been pretreated with rupatadine 10 mg once daily for 3 days. This represents a 47% ($P < 0.05$) decrease in airways caliber in patients pretreated with placebo.

Similar benefits were reported by Stuebner et al. (46) in a group of 45 patients with SAR pretreated with rupatadine 10 mg once daily or placebo for 8 days before undergoing 6-h allergen exposure in a Vienna Challenge Chamber. The results of this study are presented in Fig. 6. Rupatadine was not only very effective in relieving nasal and ocular symptoms, it was also very well-tolerated and had a rapid onset of action as indicated by statistically lower total nasal symptom scores (TNSSs) starting from the first time of assessment (15-min postexposure) compared with placebo (46).

Table 5. Summary of clinical trials with rupatadine (Rup) in patients aged 12–65 years with seasonal allergic rhinitis (SAR)

Treatment	No of patients	Duration	Study design and level of evidence*	Results and conclusions	Reference
Dose-ranging studies					
Placebo od	50	2 weeks	m, r, db, pg	Both mDTSS and DTSS _{max} were significantly lower ($P < 0.05$) with Rup 10 and Rup 20 compared with placebo. Also, patient global ratings were significantly better with Rup 10 ($P = 0.031$) and Rup 20 ($P = 0.008$). There were no significant differences between Rup 10 and Rup 20.	(60)
Rup 10 mg od	54		Level 2		
Rup 20 mg od	45				
Placebo od	A total of 392 patients were treated	2 weeks	m, r, db, pg	All doses of Rup were significantly better than placebo in alleviating symptoms based on mDTSS scores. Rup 20 was consistently the optimal dosage in terms of improvement in symptom scores while Rup10 was better in terms of investigator and patient global scores.	(28)
Rup 2.5 mg od			Level 2		
Rup 5 mg od					
Rup 10 mg od					
Placebo od	205	2 weeks	Pooled analysis	Compared with placebo all doses of Rup produced significant reductions in mDTSS: placebo (0.96); Rup 2.5 (0.8, $P = 0.0012$); Rup 5 (0.77, $P = 0.0003$); Rup 10 (0.75, $P < 0.0001$); Rup 20 (0.71, $P < 0.0001$). Rup 10 and Rup 20 were equally effective and there were no sex- or age-related differences.	(61)
Rup 2.5 mg od	76		m, r, db, pg		
Rup 5 mg od	79		Level 2		
Rup 10 mg od	541				
Rup 20 mg od	467				
Comparisons with other antihistamines					
Rup 10 mg od	124	2 weeks	m, r, db, pg	mDTSS was significantly reduced to the same score at the end of treatment (0.7) in the Rup and Cet groups. After 7 days the investigator global assessment (93% vs 84%; $P = 0.022$) and absence of runny nose (81% vs 69%; $P = 0.029$) both favored Rup suggesting a possible faster onset of action.	(63)
Cet 10 mg od	117		Level 2		
Placebo od	81	2 weeks	m, r, db, pg	mDTSS was reduced by a greater extent with Rup (33%) than with placebo (13%; $P < 0.005$) and Eba (22%; NS). Rup also produced greater improvement in individual symptoms (e.g. sneezing, nasal itching, and watery eyes) than Eba.	(64)
Rup 10 mg od	79		Level 2		
Eba 10 mg od	83				
Rup 10 mg od	112	2 weeks	m, r, db, pg,	In a per-protocol analysis mDTSS was significantly lower in the groups treated with Rup 10 (0.85) and Rup 20 (0.80) compared with Lor 10 (0.92) ($P = 0.03$). The difference was not statistically significant using an intention-to-treat analysis. Overall, based on a balance of efficacy and safety Rup 10 may be a better choice than Rup 20 or Lor 10.	(62)
Rup 20 mg od	111		Level 2		
Lor 10 mg od	116				
Rup 10 mg od	331 in total	2 weeks	m, r, db, pg	Rup 10, Rup 20 and Lor produced similar improvement in mDTSS. Regarding individual symptom scores the results were similar for the 3 treatments although they were generally better for Rup 20, the difference occasionally reaching statistical significance.	(28)
Rup 20 mg od			Level 2		
Lor 10 mg od					
Rup 10 mg od	359 in total	4 weeks	m,r,db, pg	Rup 10 and Des 5 were both significantly superior to placebo in improving mDTSS (both $P < 0.001$).	(29)
Des 5 mg od			Level 2		
Comparisons with placebo					
Placebo	30	3 days	r, db, co	Using acoustic rhinometry to objectively measure nasal congestion, Rup 10 was associated with significantly lower blockage in nasal airway caliber following allergen challenge than placebo (30%; $P < 0.05$).	(65)
Rup 10 mg od			Level 2		
Placebo	45	8 days	r, db, co	Using a 6-h allergen exposure in the Vienna Challenge Chamber subjective single and composite nasal and non-nasal symptoms were consistently significantly and statistically less severe with Rup 10 than placebo from 15 mins to the end of the 6 h test.	(46)
Rup 10 mg od			Level 2		

m, multicentre; r, randomized; db, double-blind; pg, parallel groups; co, crossover; od, once daily; mDTSS, mean daily total symptom score; DTSS_{max}, maximum DTSS; Cet, cetirizine; Des, desloratadine; Eba, ebastine; Lor, loratadine.

* See Appendix.

Perennial allergic rhinitis

Clinical studies with rupatadine in patients with moderate-to-severe PAR are summarized in Table 6 In these well-controlled trials rupatadine 10 and 20 mg once daily were significantly more effective than placebo in produc-

ing symptomatic relief, increasing the percentage of days during the study in which symptom scores were ≤ 1 (PD_{max1}) and decreasing mDTSS (28).

Compared with other antihistamines, rupatadine was shown to be at least as effective as drugs such as cetirizine, ebastine, and loratadine in relieving nasal and ocular

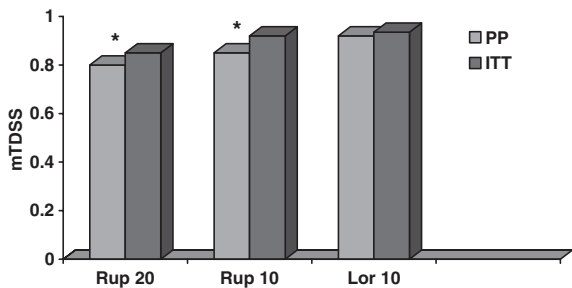


Figure 5. Mean total daily symptom scores (mTDSS) in the per protocol (PP) and intention-to-treat (ITT) populations of 339 seasonal allergic rhinitis patients treated with rupatadine (Rup) 10 mg ($n = 112$) or 20 mg ($n = 111$), and loratadine 10 mg ($n = 116$) for 2 weeks. * $P = 0.03$ vs loratadine 10 mg (adapted from Saint-Martin et al. 2004; 62).

symptoms in patients with PAR (Table 6). Overall, the various antihistamines produced similarly high levels of symptomatic relief in moderate-to-severe PAR, although some differences were observed:

- 1 Rupatadine 10 or 20 mg once daily and loratadine 10 mg once daily were equally effective in improving PD_{max1} and decreasing mDTSS. Relief of individual symptoms favored rupatadine, and the patients' impression of overall efficacy (good or excellent improvement) showed that both dosages of rupatadine were significantly better than placebo whilst loratadine was slightly worse than placebo (28).
- 2 In a similarly designed clinical trial, rupatadine 10 mg once daily and ebastine 10 mg once daily produced equivalent symptomatic relief as assessed by PD_{max1} and mDTSS scores, and both antihistamines were significantly superior to placebo (28).
- 3 Rupatadine 10 and 20 mg once daily and cetirizine 10 mg once daily all significantly increased PD_{max1} to a greater extent than placebo. Rupatadine 20 mg

appeared to have the greatest effect on symptom relief based on the consistently higher levels of statistical significance vs placebo (28).

Perez et al. (61) published a pooled analysis involving 708 patients with moderate-to-severe PAR who were treated with rupatadine 10 or 20 mg once daily, or placebo. The main finding of this study confirmed the efficacy of rupatadine in increasing PD_{max1} to a significantly greater extent with rupatadine 10 mg (45.1%, $P = 0.001$) and 20 mg (47.2%, $P < 0.0001$) compared with placebo (33.9%). Furthermore, covariate analysis found no age- or sex-related differences.

Patients classified according to ARIA criteria for allergic rhinitis

As noted in the introduction, the definition and classification of allergic rhinitis underwent a major change in 2001 following the publication of the 'ARIA' workgroup report (1, 8, 9). A small number of studies/analyses have assessed the clinical efficacy and tolerability of rupatadine in patients who met the newer ARIA classification for PER and the results are summarized in Table 7.

Persistent allergic rhinitis. Three studies have been reported evaluating the efficacy of rupatadine in patients with PER (Table 7). Roger et al. (66) investigated the longer-term efficacy (12 months) and impact on QoL of rupatadine 10 mg once daily in patients with persistent PER following a 1-month, double-blind, placebo-controlled clinical trial. Quality of life was assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). During the double-blind phase of this trial the domains of sleeping, ocular symptoms and emotions were all significantly improved by rupatadine compared with placebo. Overall, RQLQ scores continued to significantly improve from baseline values ($P < 0.0001$) over the 6- and 12-month treatment periods.

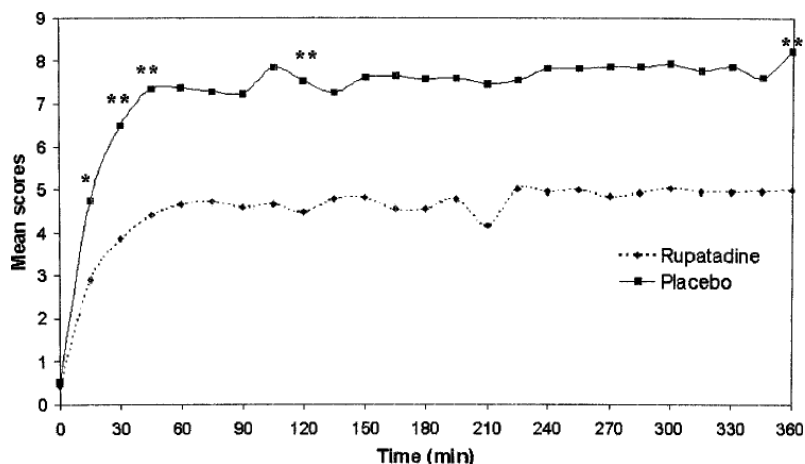


Figure 6. Mean total nasal symptom scores after allergen exposure in the Vienna Challenge Chamber following pretreatment with placebo or rupatadine in a randomised, double-blind, crossover study involving 45 patients with a history of seasonal allergic rhinitis. * $P < 0.01$; ** $P < 0.001$. (From Stuebner et al. 2006; (46) reprinted with permission from the American College of Allergy, Asthma and Immunology).

Table 6. Summary of clinical trials with rupatadine (Rup) in patients aged >12 years with a history of perennial allergic rhinitis (PAR) (28)

Treatment	No of patients	Duration	Study design and level of evidence*	Results and conclusions
Dose-ranging study				
Placebo Rup 10 mg od Rup 20 mg od	245 in total	4 weeks	m, r, db, pg Level 2	Rup 10 and Rup 20 were significantly superior to placebo in improving Pd _{max1} . A dose response relationship was not observed in this trial.
Comparisons with other antihistamines				
Placebo Rup 10 mg od Rup 20 mg od Cet 10 mg od	273 in total	4 weeks	m, r, db, pg Level 2	Rup 10, Rup 20 and Cet 10 all significantly increased Pd _{max1} compared with placebo with Rup 20 having the greatest effect. Similarly, individual symptom scores during active treatment were superior to those recorded on placebo (<i>P</i> < 0.001).
Placebo Rup 10 mg od Eba 10 mg od	219 in total	4 weeks	m, r, db, pg Level 2	Both Rup 10 and Eba 10 were associated with significantly increased Pd _{max1} and significantly decreased mean DTSS compared with placebo.
Placebo Rup 10 mg od Rup 20 mg od Lor 10 mg od	283 in total	4 weeks	m, r, db, pg Level 2	Rup 10 (48.7%) Rup 20 (50.4%) and Lor 10 (48.6%) all increased Pd _{max1} more than placebo (34.1%). Only the increase with Rup 20 reached statistical significance. All active treatments reduced mean DTSS score statistically significantly (<i>P</i> < 0.05) compared with placebo. Rup produced better control of individual symptoms than Lor and it also was associated with higher scores for patient global impression.

m, multicentre; r, randomized; db, double-blind; pg, parallel groups; od, once daily; Pd_{max1}, the % of days on which the most severe symptom score was ≤ 1; mDTSS, mean daily total symptom score; Cet, cetirizine; Eba, ebastine; Lor, loratadine.

* See Appendix.

Table 7. Summary of clinical trials with rupatadine (Rup) in patients with persistent allergic rhinitis (PER) classified according to ARIA criteria

Treatment	No of patients	Duration	Study design and level of evidence*	Results and conclusions	References
Rup 10 mg od	167	2 weeks	m, o	Rup 10 significantly (<i>P</i> < 0.001) reduced nasal symptoms such as rhinorrhoea, nasal itching, sneezing, nasal congestion, and total nasal symptoms. The positive effects usually commenced on days 1 or 2 of treatment.	(59)
Placebo Rup 10 mg od	320 in the db study and 92 in the 1-year study	12 months	m, r, db, pc, 4 weeks then m, o Level 2	During the 1-month db phase based on findings from RQLQ, Rup 10 significantly improved the domains of sleeping, ocular symptoms, and emotions compared with placebo. RQLQ overall scores were significantly (<i>P</i> < 0.001) improved by Rup 10 at 6 and 12 months. Long-term therapy with Rup 10 mg was effective in alleviating symptoms and improving QoL.	(66)
Placebo Rup 10 mg od Cet 10 mg od	185 175 183	12 weeks	m, r, db, pg Level 2	After 12 weeks treatment Rup 10 significantly reduced TSS compared with placebo (48% vs 39%; <i>P</i> < 0.001). The difference between Cet and placebo was not statistically significant. The onset of action for Rup was on day 2 (Rup vs Placebo; <i>P</i> = 0.013). Both Rup and Cet were superior to placebo in improving secondary end points such as 4 and 8 week TSS, sneezing, and nasal pruritus and Rup also improved nasal discharge. QoL as measured by RQLQ was significantly improved from baseline with Rup and Cet compared with placebo after 12 weeks treatment.	(67)

m, multicentre; r, randomized; db, double-blind; pg, parallel groups; o, open; od, once daily; TSS, total symptom score; QoL, quality of life; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; Cet, cetirizine.

* See Appendix.

Fantin et al. (67) compared rupatadine 10 mg once daily with cetirizine 10 mg once daily in a large multicentre, double-blind, placebo-controlled clinical trial involving 543 patients with moderate-to-severe PER. After 12 weeks' treatment, the change in total symptom scores (TSS) from baseline was significantly lower with rupatadine compared with placebo (*P* < 0.01) whereas the reduction with cetirizine did not achieve statistical

significance. Both rupatadine and cetirizine were significantly better than placebo with regards improvement in secondary variables such as 4- and 8-week TSS, nasal pruritus and sneezing, and rupatadine was also better than placebo in reducing total nasal symptoms and nasal discharge. In addition, and compared with placebo, rupatadine produced significantly greater improvements in total RQLQ and in most of the individual domains

(activities, sleep, nasal symptoms, and ocular symptoms). Similar improvements in QoL were documented for cetirizine. Again, in this clinical trial, rupatadine was shown to have a rapid onset of action with TSS reduced to a significantly greater extent than placebo after only 2 days ($P < 0.05$).

In an open, multicentre trial involving 167 patients with moderate-to-severe persistent PER in Brazil, Mion et al. (59) found that rupatadine 10 mg once daily for 14 days provided significant symptomatic relief on days 7 and 14 for rhinorrhoea, nasal itching, sneezing, nasal congestion and total nasal symptoms. Patient assessments of symptom severity from days 1 to 2 onwards were also significantly reduced by rupatadine.

Chronic idiopathic urticaria

The efficacy of rupatadine has recently been evaluated in two clinical trials and one pooled analysis in patients with moderate-to-severe CIU (Table 8). The term CIU has been extensively used in the literature, but the symptomatology would now come under the subheading of ‘spontaneous urticaria’ according to recent EAACI recommendations (22, 23).

In the most recent and largest trial to date, Gimenez-Arnau et al. (68) compared rupatadine once daily with placebo in a randomized, double-blind trial of 6-week duration. Rupatadine 10 and 20 mg reduced mean pruritus severity (MPS) scores (from baseline) by 57% and 63%, compared with 44% for placebo at 4 weeks (the primary outcomes measure). This beneficial effect was evident from week 1 and was maintained throughout the 6-week trial at which time MPS scores were reduced by 59% (R 10 mg), 66% (R 20 mg) and 49% (placebo). Importantly, there was a clear difference in favor of

rupatadine 10 and 20 mg over placebo ($P = 0.013$ and $P < 0.0001$, respectively) after the first dose, highlighting its fast onset of action. Rupatadine also produced significant improvements in secondary outcomes such as mean number of wheals (MNWs; week 4) and mean TSS (calculated as the sum of MPS and MNW on weeks 4 and 6) compared with placebo. Quality of life, as determined by the Dermatology Life Quality Index (DLQI), demonstrated that both dosages of rupatadine significantly improved all but one of the individual DLQI subdomains after 2 weeks’ treatment, compared with placebo. These results suggest that rupatadine provides rapid and meaningful QoL benefits in patients with CIU.

In an earlier phase 2 clinical trial rupatadine at dosages of 5, 10, and 20 mg once daily was compared with placebo over a period of 4 weeks (69). Rupatadine 10 and 20 mg significantly reduced MPS scores by 62% ($P < 0.05$) and 72% ($P < 0.001$), respectively, from baseline values. These decreases were significantly ($P < 0.05$) greater than the 46% reduction produced by placebo. Rupatadine 5 mg once daily reduced MPS score by 52% vs baseline and this effect was not statistically different from that achieved by placebo. The evaluation of weekly MPS scores indicated that rupatadine decreased pruritus in a dose- and time-dependent manner (Fig. 7) The improvement in MPS was mirrored by a linear reduction in the MNWs which were 30%, 34%, 45%, and 58% for placebo and 5, 10, and 20 mg rupatadine, respectively. Whilst these improvements did not reach statistical significance there was a tendency for a time-dependent effect as shown by the suppression of wheals on weeks 3 and 4, with a significant suppression in MNW by about 60% in patients treated with rupatadine 20 mg. Both rupatadine 10 and 20 mg significantly

Table 8. Summary of clinical trials with rupatadine (Rup) in patients aged 12–65 years with a history of chronic idiopathic urticaria (CIU)

Treatment	No of patients	Duration	Study design and level of evidence*	Results and conclusions	References
Placebo Rup 5 mg od Rup 10 mg od Rup 20 mg od	69 68 73 67	4 weeks	m, r, db, pg Level 2	Rup 10 and Rup 20 significantly ($P < 0.05$) reduced pruritus severity (from baseline) by a greater amount than placebo (63% vs 72% vs 46%, respectively). This was mirrored by a linear reduction in the mean number of wheals: 30%, 34%, 45%, and 58% for placebo, Rup 5, Rup 10, and Rup 20 respectively. Mean TSS were significantly improved by Rup 10 and Rup 20 compared with placebo. Patient and investigator global assessments of efficacy significantly favored all doses of Rup.	(69)
Placebo Rup 10 mg od Rup 20 mg od	111 110 108	6 weeks	m, r, db, pg Level 2	Rup 10 and Rup 20 significantly ($P < 0.05$ and $P < 0.001$) reduced pruritus severity (from baseline) by a greater amount than placebo (59% vs 66% vs 49%). Rup also produced significant improvements in secondary outcomes such as mean TSS, mean number of wheals and measures of QoL. There were no significant differences between Rup 10 and Rup 20 in terms of efficacy and given its better tolerability profile Rup 10 is the preferred dosage.	(68)
Placebo Rup 10 mg od Rup 20 mg od	182 186 179	4 weeks	Pooled data, m, r, db, pg Level 2	Rup 10 and Rup 20 significantly ($P < 0.01$ and $P < 0.001$) reduced pruritus severity (from baseline) by a greater amount than placebo (38% vs 42% vs 24%) after only 12 h. This effect was maintained after 7 days of treatment and throughout the study (4 weeks).	(70)

m, multicentre; r, randomized; db, double-blind; pg, parallel groups; od, once daily; TSS, total symptom score; QoL, quality of life.

* See Appendix.

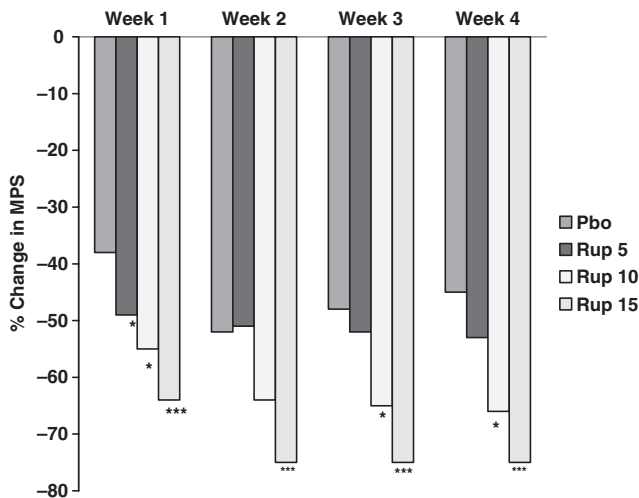


Figure 7. Percentage change in mean pruritus score (MPS) with time in patients with moderate-to-severe chronic idiopathic urticaria treated with placebo (Pbo; $n = 69$), or rupertadine (Rup) 5 mg ($n = 68$), 10 mg ($n = 73$), or 20 mg ($n = 67$) for 4 weeks. * $P < 0.05$ vs placebo; *** $P < 0.0001$ vs placebo. (Adapted from Dubertret et al. 2007; 69).

reduced mean TSS from baseline values to a much greater extent than placebo (55% and 66% vs 39%, respectively; $P < 0.05$ for both dosages vs placebo). Overall clinical response and global CIU assessments (investigator and patient), interference with sleep and performance of daily activities, all improved with rupertadine 10 and 20 mg.

The pooled analysis performed by Gimenez-Arnau et al. (70) highlighted the rapid onset of action rupertadine 10 and 20 mg compared with placebo (see section Fast onset of action of rupertadine) and confirmed the significant improvement in MPS scores after 7 days and throughout the 4-week study period. A complete responder analysis of this data again showed that rupertadine 10 and 20 mg were significantly superior to placebo in terms of different responder criteria such as the percentage of patients achieving a 50% improvement in symptom scores, the percentage of patients achieving a 75% improvement and the percentage of patients achieving a result better than the lower confidence limit for the mean (LCLM) for placebo. In the LCLM analysis rupertadine 20 mg produced a greater improvement in all scores with statistically significant differences observed for a 75% reduction in MPS and mean TSS compared with rupertadine 10 mg (71). These results support the use of higher dosages of rupertadine in patients with chronic urticaria.

Fast onset of action of rupertadine

From the patient's perspective, rapid relief of symptoms and the return to a 'normal' life would be an ideal property for medicines used to treat allergic rhinitis and chronic urticaria. Interestingly, in clinical trials with

rupertadine many groups reported its fast onset of action in patients with seasonal rhinitis (46, 63, 64), perennial rhinitis (28), persistent rhinitis (59, 67), and CIU (68, 69). This is consistent with the pharmacokinetic profile of rupertadine, which was shown to be rapidly absorbed with peak plasma concentrations being attained in < 1 h (see Table 1).

Examples of specific data relating to the onset of antihistaminic activity and symptom relief include:

- 1 In the Vienna Challenge Chamber rupertadine significantly ($P < 0.01$) reduced mean TNSSs compared with placebo from the very first evaluation at 15 min after challenge (Fig. 5). This very rapid response compared favorably with results for other antihistamines such as loratadine and levo-cetirizine that had previously been tested in this system (46).
- 2 Compared with cetirizine, rupertadine produced significantly greater improvement in the symptom of runny nose ($P = 0.03$) and was ranked better by investigators ($P = 0.02$) after 7 days' treatment leading Martinez-Cócera et al. to suggest that it might have a faster effect (63).
- 3 In patients with PER, rupertadine relieved symptoms (as indicated by reduced TSS or patient diary records) from as early as the first or second day of treatment (59, 65, 67).
- 4 In patients with moderate-to-severe CIU rupertadine 10 and 20 mg both significantly improved MPS ($P = 0.013$ and $P < 0.0001$, respectively) compared with placebo within 24 h of taking the first dose, which is indicative of a fast onset of action (68).

Figure 8 highlights the findings from a formal analysis of pooled data from 2 double-blind placebo-controlled studies involving a total of 582 patients with CIU, which assessed the time point at which rupertadine 10 and 20 mg did produce significant relief of pruritus and number of wheals. The results of this study clearly showed that both dosages of rupertadine administered once daily rapidly relieved pruritus (which is the most troubling symptom associated with chronic urticaria (70)). Statistically significant relief of pruritus was achieved within 12 h of administration of the first dose compared with placebo and baseline MPS scores.

Conclusions

- 1 Clinical trials with rupertadine have clearly shown that it is an effective and well-tolerated treatment for allergic rhinitis and CIU.
- 2 Rupertadine has a fast onset of action, producing rapid symptomatic relief.
- 3 It also has an extended duration of clinical activity, which allows once-daily administration.

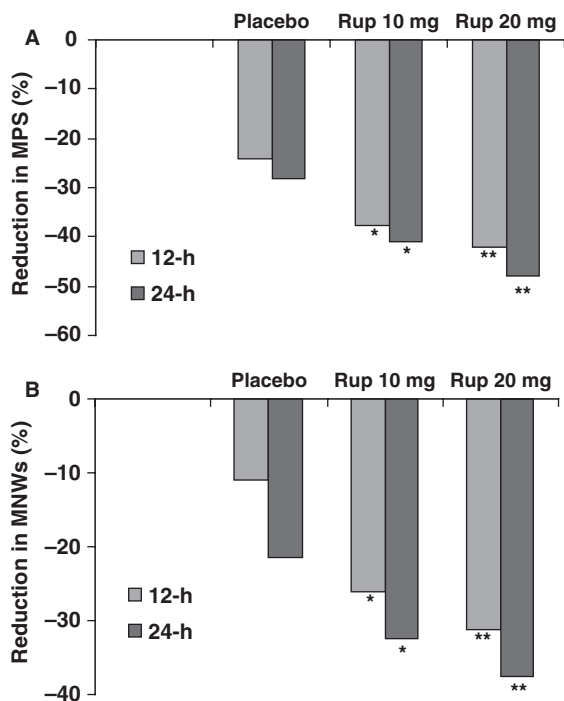


Figure 8. Reduction in mean pruritus score (MPS) and mean number of wheals (MNWs) 12- and 24-h after treatment with placebo, and rupatadine (Rup) 10 and 20 mg once daily in a pooled analysis involving 582 patients with chronic idiopathic urticaria. **P* < 0.01 and ***P* < 0.001 vs corresponding placebo value. (Adapted from Gimenez-Arnau et al. 2007; 70).

- 4 In all studies, rupatadine was significantly superior to placebo.
- 5 In comparative clinical trials, rupatadine was shown to be at least as effective as drugs such as loratadine, cetirizine, desloratadine and ebastine in reducing allergic symptoms in adult/adolescent patients with seasonal, perennial or persistent allergic rhinitis.
- 6 Rupatadine also produced significantly greater symptomatic relief than placebo in patients with CIU. Clinical benefit was evident from the first day of treatment and extended throughout the duration (up to 6 weeks) of the various clinical trials.

What aspects of the pharmacological and clinical activity of rupatadine impact on its long-term use in everyday life?

For any medical condition, pharmacological intervention is aimed at curing, alleviating or preventing recurrences of the disease, and primary end-points usually include: prevention of mortality, reduction of future morbidity and improvement in patient’s well-being. For patients with rhinitis and chronic urticaria, the primary goal of treatment is usually aimed at improving their well-being/health-related QoL (72). Antihistamines are well-established first-line treatment options in allergic disorders and

consequently, it is important to understand the effect that new compounds have on the patient; not just in terms of symptom relief, which is clearly very important, but also taking a more ‘holistic view’. In other words, how does the treatment impact on everyday life? To assess this we must address certain questions related to clinical benefits of treatment such as:

- 1 How convenient is treatment with rupatadine? Is it simple to use? What are the contraindications to its use, if any? How effective is it?
- 2 How safe is rupatadine both in the short- and long-term, and given previous experience with antihistamines such as terfenadine and astemizole, how does the new product effect cardiac function/rhythm?
- 3 As sedation is a common side-effect associated with many first generation antihistamines, and this negatively impacts QoL by precluding patients from undertaking tasks requiring mental alertness (driving, operating machinery, etc), what is the evidence concerning the lack of negative CNS effects?
- 4 And finally, are there tools available to clinicians, which can help them assess the impact of treatment on the well-being and QoL of patients suffering from allergic rhinitis and chronic urticaria?

Convenience of treatment

Rupatadine fumarate is currently approved for the treatment of SAR, PAR, and chronic urticaria in adolescents and adults. The drug is administered orally once daily with or without food and this represents a very straightforward and convenient dosage schedule for all patients. With regards to its pharmacokinetic properties, rupatadine achieves maximal plasma concentrations very quickly, which enables it to produce rapid symptom relief. The drug also has an extended duration of action, which facilitates once daily administration, and it is thought that this results from its metabolism to active metabolites (Table 1).

Another factor influencing convenience of administration is the potential interaction of rupatadine with other drugs or foods. As noted in Table 1 rupatadine is metabolized via microsomal pathways involving cytochrome P450 isoenzyme 3A4 (CYP3A4) and it might potentially interact with drugs/foods that are metabolized via the same system (e.g. ketoconazole, erythromycin, fluoxetine, grapefruit juice). Pharmacokinetic studies involving rupatadine and these agents have been undertaken and reviewed elsewhere (28–30) with the following main findings:

- 1 Ketoconazole 200 mg once daily for 7 days inhibited both the presystemic and systemic metabolism of rupatadine 20 mg once daily, resulting in a 10-fold increase in the systemic exposure of rupatadine but less exposure to its metabolites. Despite this large

increase in rupatadine plasma levels no clinically relevant changes in ECG parameters, QTc interval, laboratory tests, vital signs, or adverse events were observed (28–30).

- 2 Erythromycin 500 mg three times daily for 7 days reduced the presystemic metabolism of rupatadine 20 mg once daily increasing its systemic exposure two- to three-fold. However, erythromycin had little impact on elimination half-life or on the metabolites of rupatadine (28–30).
- 3 In contrast, no clinically relevant alterations in pharmacokinetic parameters were documented when rupatadine 10 mg and azithromycin (500 mg at once then 250 mg) were co-administered once daily for 6 days (73).
- 4 Similarly no clinically relevant interaction was observed when therapeutic dosages of rupatadine and fluoxetine were co-administered (29).
- 5 Co-administering rupatadine with grapefruit juice resulted in a three-fold increase in systemic exposure of the antihistamine whereas exposure to its metabolites was unaffected (29).
- 6 Systemic exposure to rupatadine was increased 23% after food compared with taking the drug under fasting conditions. This change appeared to be of little clinical consequence (74).
- 7 Although the combination of ethanol and antihistamines impaired cognitive and psychomotor performance, the effect with rupatadine 10 mg was not significant compared with ethanol alone, and less than that documented for cetirizine and hydroxyzine (75).

The results of these clinical studies indicate that rupatadine does interact with drugs and foods that are metabolized via oxidative microsomal pathways, particularly those involving the CYP3A4 enzyme. Whilst the interactions appear to be of limited clinical relevance, it is prudent to avoid co-administration of this newer antihistamine with drugs and foods such as ketoconazole, erythromycin, and grapefruit juice.

Tolerability and safety

Adverse effects. Results from published phase III clinical trials with rupatadine have recently been independently reviewed by Picado (29) and Keam & Plosker (30) and both concluded that the antihistamine was well-tolerated, and at a dosage of 10 mg once daily it was not significantly different to placebo. Picado (29) presented data from a total of 3340 patients or healthy volunteers who received rupatadine 10 mg (*n* = 2025) or placebo (*n* = 1315) during clinical trials (Table 9). Overall, rupatadine was well-tolerated and most adverse effects were of mild-to-moderate severity and in this analysis somnolence was the most commonly reported adverse effect (9.5% vs 3.4% for placebo) followed by headache (6.8% vs 5.6%) and fatigue (3.3% vs 2.0%).

Table 9. Most common treatment-related adverse events reported during clinical trials involving patients treated with rupatadine 10 mg once daily (*n* = 2025) or placebo (*n* = 1315) (29)

Adverse event	Rupatadine-treated patients (<i>n</i> = 2025)	Placebo-treated patients (<i>n</i> = 1315)
Somnolence	9.5	3.4
Headache	6.8	5.6
Fatigue	3.2	2.0
Asthenia	1.5	0
Dry mouth	1.2	0
Dizziness	1.0	0

In comparative clinical trials, rupatadine 10 or 20 mg once daily was as well-tolerated as drugs such as loratadine 10 mg (28, 62), ebastine 10 mg (28, 64), or cetirizine 10 mg all administered once daily (28, 63, 67).

Of particular interest is a 1-year open-label study involving 120 patients with PER, and which was designed to comply with International Conference on Harmonisation (ICH) (76) and European Medicines Agency (EMA) (77) guidelines for testing the safety of drugs for long-term use. Of the recently introduced antihistamines rupatadine is one of the first to have such extended long-term safety data, and the results of this trial confirmed its excellent tolerability, which was consistent with findings from shorter-term clinical trials (78). There was clear evidence that with time the incidence of adverse effects decreased with rupatadine 10 mg once daily (Table 10). Furthermore, no clinically relevant ECG or laboratory changes were reported during this clinical trial.

A pooled analysis of results from clinical trials involving 617 patients with CIU demonstrated no clinically significant difference between various dosages of rupatadine (Rup) and placebo (79). The most frequently reported adverse effects were headache (placebo 2.75%; Rup 5 mg 2.86%; Rup 10 mg 2.69%; Rup 20 mg 3.91%) and somnolence (placebo 3.85%; Rup 5 mg 4.29%; Rup 10 mg 3.76%; Rup 20 mg 13.41%). Again, no clinically significant ECG, laboratory or vital sign adverse events were documented in this analysis.

Cardiac safety. Prolongation of the QTc interval on the ECG and the development of *torsades de pointes*-type arrhythmias were reported in the literature for astemizole

Table 10. Long-term (6-month and 1-year) safety data for rupatadine 10 mg once daily used in the treatment of patients with mild-to-moderate allergic rhinitis (78)

Adverse events (AEs)	Duration of treatment	
	6 months (<i>n</i> = 324, %)	12 months (<i>n</i> = 120, %)
Patients with ≥1 AE	74	66
Patients with drug-related AE	20.4	10.8
Somnolence	7.7	5.8
Headache	6.5	0.8
Dry mouth	2.2	0.8

and terfenadine during the 1990s, and this has led to wider concern regarding the cardiotoxic potential of the antihistamines in general (80, 81). This effect is dependent upon a direct blockade of a specific class of potassium channel controlling the repolarization of the cardiac action potential and as such, it is not related to blockade of the H₁-receptor and therefore not a class effect (1). Nevertheless, preclinical and clinical evaluation of possible cardiotoxicity is a prerequisite for the regulatory assessment of such drugs before they can enter the market.

Cardiac safety has been extensively assessed as part of the clinical evaluation of rupatadine. A total of 6450 ECGs from 4000 healthy volunteers and 2450 adult patients with allergy have been analyzed as part of this programme (28). Rupatadine dosages in these studies ranged from 2.5 to 80 mg either as single dose or once daily for 2–4 weeks and were tested under a range of conditions: with or without food; administered alone or concomitantly with alcohol, erythromycin, or ketoconazole; and in young and elderly healthy volunteers of both sexes. In this evaluation, rupatadine produced no clinically relevant changes in QT/QTc intervals despite the fact that drugs which increase the systemic exposure of the antihistamine (erythromycin and ketoconazole are potent cytochrome P450 3A4 isoenzyme inhibitors) were co-administered.

More recently, the effect of rupatadine on QTc interval was assessed in accordance with EMEA and ICH Guidelines (ICH E14): a 'Thorough QT/QTc study' (82). This was a randomized, double-blind, placebo-controlled clinical trial in 160 healthy volunteers designed to determine whether rupatadine had a significant effect on cardiac repolarization as assessed by QT/QTc interval prolongation. Moxifloxacin, which is known to increase the QTc interval, was used as a positive control in this study and it produced the expected prolongation of QTc duration. Importantly, rupatadine at dosages of 10 mg (recommended) and 100 mg (10 times recommended) daily, had no statistically or clinically significant effect on cardiac repolarization. Furthermore, there was no gender effect, no pharmacodynamic/pharmacokinetic relationship, and no QTc outliers suggestive of an effect of rupatadine on QTc duration.

Preclinical evaluation of the cardiovascular effects of rupatadine has been widely reviewed elsewhere (28–30) and also highlighted the fact that it has no clinically relevant effects on the cardiovascular system as shown by:

- 1 A dose of > 100 times that recommended in humans had no effect on ECG parameters (QTc, PR or QRS intervals), mean blood pressure (BP) and heart rate in rats, guinea pigs and dogs (28, 29, 83). Furthermore, rupatadine was not associated with arrhythmias or an increased rate of cardiovascular mortality in these studies. In guinea pigs, rupatadine did not alter ECG or haemodynamic parameters. Likewise, loratadine did not affect the ECG, but it was associated with significant changes in BP and heart rate in this model (84).
- 2 After oral administration of 20 mg/kg (about 100 times the therapeutic dose) there was no evidence of selective accumulation in rat cardiac tissue (85).
- 3 Rupatadine and one of its main metabolites (3-hydroxydesloratadine) did not affect the cardiac action potential in *in vitro* isolated dog Purkinje fibers at concentrations at least 2000 times greater than the C_{max} reached after administration of a 10 mg dose in humans (83).
- 4 *In vitro*, rupatadine concentrations required to block human ether-a-gogo-related gene (HERG) potassium channel or the human-cloned hKv1.5 potassium channel expressed in a mouse L-cell line were almost 2000-fold greater than serum concentrations determined after administering rupatadine 10 mg to human volunteers (28, 30, 86).

Lack of CNS effects

Sedation is a common side-effect associated with many first generation antihistamines, and this negatively impacts QoL by precluding them from undertaking tasks requiring mental alertness (driving, operating machinery, etc.). Antihistamines which do not cause sedation will clearly be more advantageous.

Consistent with the selectivity of rupatadine for peripheral H₁-receptors (see section Antihistaminic activity), CNS activity determined by EEG activity and motor activity was unchanged in rat and murine models following administration of intravenous doses of rupatadine up to 30 mg/kg and oral doses up to 100 mg/kg (37, 39). Similar results were recorded for loratadine in these experimental studies. Furthermore, like terfenadine, rupatadine did not potentiate pentobarbital-induced anaesthesia in mice whereas loratadine increased sleeping times almost three-fold (37).

In humans, psychomotor activity was not significantly affected by rupatadine 10 or 20 mg (48). However, at higher doses there was dose-dependent impairment, with rupatadine 40 mg producing mild deterioration and rupatadine 80 mg producing much more significant impairment which was similar to that caused by hydroxyzine 25 mg (48). In combination with ethanol, rupatadine 10 mg did not produce greater cognitive/psychomotor impairment compared with ethanol alone, whereas a higher dose (20 mg) and therapeutic doses of cetirizine (10 mg) and hydroxyzine (25 mg) did result in greater cognitive and psychomotor decline compared with ethanol alone (75). Similarly, administration of rupatadine 10 mg did not result in any significant changes in mental ability nor did it potentiate lorazepam-induced mental impairment (87).

In a practical assessment of 'mental alertness' rupatadine 10 mg was compared with hydroxyzine 50 mg in a placebo-controlled clinical trial in which 20 healthy volunteers performed a car driving test (88). In various

measures of driving performance such as standard deviation of lateral position, standard deviation of speed, standard deviation of headway, brake reaction time and driving quality ratings rupertadine did not differ from placebo whereas hydroxyzine was associated with impairment equivalent to that produced by a blood alcohol level of 0.9%.

Patient well-being and QoL

There is now very little doubt that there is significant impairment of QoL in patients with allergic rhinitis and chronic urticaria (6, 11, 89, 90). Although generally not life-threatening, in their severest forms, allergic disorders can profoundly impact many aspects of everyday life and patients may be affected by poor sleeping patterns, emotional problems, impairment of physical and mental functioning, and disturbances in daily activities (90). In the respiratory area various studies have demonstrated that the disease order for the magnitude of impairment is SAR < moderate asthma = perennial rhinitis = persistent rhinitis < severe asthma (89).

In patients with PER, health-related QoL was assessed using the RQLQ (66, 67). In a 12-week study both rupatadine 10 mg once daily and cetirizine 10 mg once daily significantly ($P < 0.05$) improved total RQLQ scores compared with placebo. Rupatadine significantly improved the domains of 'sleep' ($P < 0.05$), 'activities' ($P < 0.01$) and 'nasal symptoms' ($P < 0.01$) compared with placebo while cetirizine significantly improved the domains of 'activities', and 'nasal' and 'eye' symptoms compared with placebo (67). In a long-term study rupatadine significantly improved overall RQLQ scores compared with baseline values ($P < 0.0001$) following treatment for 6 and 12 months (66). After 12 months' follow-up the domains of 'nasal symptoms', 'practical

problems' and 'activities' provided a moderate improvement in QoL for patients.

In 334 patients with moderate-to-severe CIU the impact of rupatadine 10 or 20 mg once daily for 6 weeks on health-related QoL was assessed using the DLQI in a placebo-controlled trial (68, 91). Rupatadine 20 mg significantly ($P < 0.005$) decreased DLQI from baseline by 26.6% after 4 weeks and 29.2% after 6 weeks. This was associated with a significant improvement in the level of general discomfort, compared with placebo, as determined by the change in visual analogue scores from baseline values (68) Compared with placebo, assessment of the individual domains of the DLQI showed that both dosages of rupatadine significantly ($P < 0.05$) improved all scores after 2 weeks of treatment except for 'leisure' and 'personal relationships' in the rupatadine 10 mg group. Results after 4 weeks' treatment are shown in Fig. 9. Time-dependent analysis demonstrated progressive improvement in all sub-domains with both rupatadine 10 and 20 mg once daily, with only isolated cases not achieving statistical significance vs placebo.

Conclusions

- 1 Rupatadine is administered orally once daily with or without food and this represents a very straightforward and convenient dosage schedule.
- 2 In clinical trials, it has been well-tolerated with somnolence and headache being the most frequently reported adverse events, and in comparative studies no significant differences were observed between rupatadine and other antihistamines such as loratadine, cetirizine, and ebastine.
- 3 Rupatadine has undergone long-term testing (up to 1-year) in compliance with ICH and EMEA guidelines and this confirmed its good tolerability.

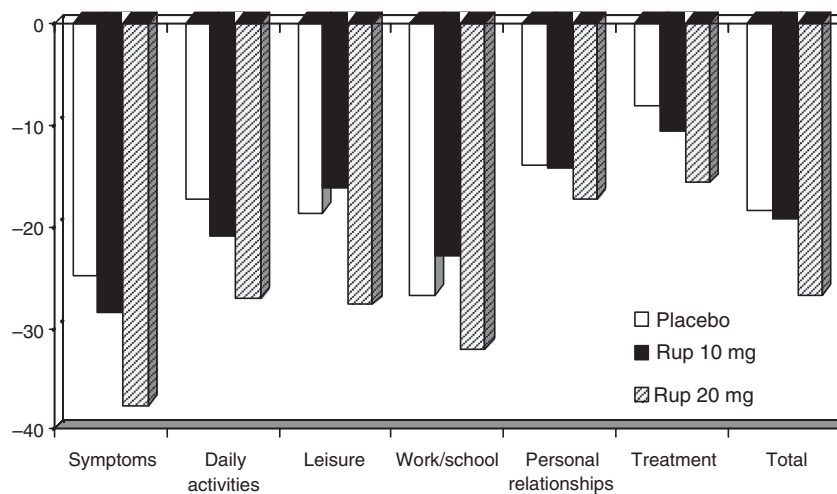


Figure 9. Decrease in DLQI sub-domain scores in patients with CIU treated with placebo (n = 111), rupatadine (Rup) 10 mg (110), and 20 mg (108) for 4 weeks (adapted from Gimenez-Arnau et al. 2007; 68).

- 4 Importantly, rupatadine showed no adverse cardiovascular effects in preclinical or extensive clinical testing, nor negative significant effects on cognition or psychomotor performance (including a practical driving study).
- 5 Rupatadine does interact with drugs and foods that are metabolized via oxidative microsomal pathways, particularly those involving the CYP3A4 enzyme. Whilst the interactions appear to be of limited clinical relevance it is prudent to avoid co-administration of this newer antihistamine with drugs and foods such as ketoconazole, erythromycin, and grapefruit juice.
- 6 Questionnaires employed to assess the overall well-being of patients with allergic rhinitis or CIU have demonstrated positive and significant trends in favor of rupatadine. These mirror findings from clinical trials, which generally reported high patient global rating scores.

New-generation antihistamines: the role of rupatadine in clinical practice

From a pharmacological perspective the development of the H₁-receptor antagonists (H₁ antihistamines) has been a steady evolution based on a classical receptor agonist/antagonist model. Today we have a better understanding of the mechanism of action of the antihistamines and they appear to act on the H₁-receptor in a positive way (agonistic) and they are now considered to be inverse agonists (92–94). It is also recognized that all the histamine receptor subtypes are G-protein-coupled receptors which can exist in an active or inactive state that co-exist in a reversible equilibrium. The antihistamines bind to the receptor and stabilize it in the inactive conformation (92).

The goal of developing more effective and/or safer antihistamines has been driven by the prominent role played by histamine in the pathophysiology of common disorders such as allergic rhinitis and chronic urticaria. First-generation antihistamines were developed for their ability to antagonize the H₁-receptor rather than a predefined scientific attempt to modulate the allergic process/inflammatory response, and led to the introduction of drugs such as chlorphenamine (chlorpheniramine) and promethazine. These agents were very effective and potent antihistamines, but they were associated with significant adverse effects, most notably sedation and impaired psychomotor activity (92). As a result of the detrimental effects on performance and psychomotor activity the focus turned to the development of 'non-sedating' antihistamines. The culmination of this research led to the introduction of drugs such as astemizole, cetirizine, ebastine, loratadine, mizolastine, and terfenadine, which had significantly reduced effects on the CNS, and they were widely used in the treatment of rhinoconjunctivitis and urticaria. However, in the 1990s two of the second-generation antihistamines (astemizole and terfen-

adine) were associated with QTc prolongation and occasional episodes of the life-threatening *torsades de pointes*. Today, the metabolites of some of the original second-generation products have been introduced into the marketplace (e.g. desloratadine, fexofenadine, and levocetirizine), as they have proven much safer than the parent compounds (loratadine, terfenadine, and cetirizine, respectively) (93, 94). These have been joined by newer antihistamines such as rupatadine which was developed with the goal of creating a powerful H₁-blocker without CNS- or cardiotoxic side-effects.

Rupatadine is an interesting antihistamine as it is dual antagonist, inhibiting both histamine H₁- and PAF-receptors. In preclinical pharmacological testing rupatadine was also shown to modulate other components of the inflammatory process such as mast cell degranulation (provoked by both immunological and nonimmunological stimuli), eosinophil and neutrophil chemotaxis, cytokine (IL-5, IL-6, IL-8, GM-CSF and TNF- α) production, and neutrophil adhesion molecule (CD11b and CD18) expression.

Clinical evaluation of rupatadine thus far has been focussed in two clinical settings where antihistamines have traditionally been first-line treatment options; allergic rhinitis and chronic urticaria. In well-controlled clinical trials in patients aged ≥ 12 years with allergic rhinitis (SAR, PAR, or PER), rupatadine 10 or 20 mg once daily produced significantly greater symptomatic relief than placebo. In comparative clinical trials rupatadine was shown to be at least as effective as drugs such as desloratadine, loratadine, cetirizine, and ebastine in reducing nasal and ophthalmic symptoms in adult/adolescent patients with allergic rhinitis. Rupatadine also produced significantly greater symptomatic relief than placebo in patients with chronic urticaria. Clinical benefit was evident from the first day of treatment and extended throughout the duration (up to 6 weeks) of the various clinical trials.

Allergic rhinitis and chronic urticaria are associated with significant impairment of QoL. Importantly, in studies which employed questionnaires to assess the overall well-being of patients with allergic rhinitis or chronic urticaria it was demonstrated that rupatadine produced significant benefits compared with placebo. These findings mirror results from clinical trials which generally reported high patient global rating scores. A possible contributing factor to QoL perception is how rapidly the medication produces symptomatic relief. Interestingly, in clinical trials with rupatadine many groups reported its fast onset of action in patients with seasonal rhinitis, perennial rhinitis, persistent rhinitis and CIU. This is consistent with the pharmacokinetic profile of rupatadine which was shown to be rapidly absorbed with peak plasma concentrations being attained in less than an hour.

In clinical trials rupatadine has been well-tolerated and in comparative studies no significant differences were observed between rupatadine and other antihistamines

such as loratadine, cetirizine, and ebastine. Extensive clinical evaluation, including long-term studies (up to 1-year), have confirmed the cardiovascular safety at usual (10–20 mg once daily) and higher dosages (up to 80 mg) of this newer antihistamine. Furthermore, it has no significant effect on cognition, driving or psychomotor performance at usual therapeutic doses. Rupatadine has the potential to interact with drugs and foods that are metabolized via oxidative microsomal pathways, particularly those involving the CYP3A4 enzyme, but the interaction appears to be of limited clinical relevance. However, it is prudent to avoid co-administration with drugs and foods such as ketoconazole, erythromycin, and grapefruit juice.

In conclusion, the evolution of the antihistamine class of drugs has resulted in the development of effective and

safer products for treating a large population of patients who suffer from disorders such as allergic rhinitis and chronic urticaria which have a significant negative impact on QoL. Rupatadine is one of the most recently introduced products in this class, and it has been shown to be an effective and generally well-tolerated treatment for allergic rhinitis and chronic urticaria. It possesses anti-inflammatory effects in addition to dual blockade of H₁- and PAF-receptors, and the clinical relevance of these remains to be clarified.

Acknowledgment

Editorial assistance was kindly provided by Steve Clissold PhD, Content Ed Net, Madrid, Spain.

References

- Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(Suppl. 5):S147–S334.
- Holgate ST, Canonica GW, Simons FER, Taglialetela M, Tharp M, Timmerman H et al. Consensus group on new-generation antihistamines (CONGA): present status and recommendations. *Clin Exp Allergy* 2003;**33**:1305–1324.
- Howarth PH, Holmberg K. Allergic rhinitis an increasing clinical problem. *Allergy* 1995;**50**:4–5.
- Weiss ST. Eat dirt – the hygiene hypothesis and allergic diseases. *New Engl J Med* 2002;**347**:930–931.
- AAAAI, The Allergy Report. Available at: <http://www.theallergyreport.com> (accessed January 2008).
- Meltzer EO. Does rhinitis compromise night-time sleep and daytime productivity? *Clin Exp All Rev* 2002;**2**:67–72.
- Potter PC. Effectiveness and safety of new-generation antihistamines in allergic rhinitis and urticaria. *SA Fam Pract* 2005;**47**:24–28.
- Bousquet J, Van Cauwenberge P, Bachert C, Canonica GW, Demoly P, Durham R et al. Requirements for medications commonly used in the treatment of allergic rhinitis. *Allergy* 2003;**58**:192–197.
- Bousquet J, Van Cauwenberge P, Khaled NA, Bachert C, Baena-Cagnani CE, Bouchard J et al. Pharmacologic and anti-IgE treatment of allergic rhinitis (ARIA) update (in collaboration with GA²LEN). *Allergy* 2006;**61**:1086–1096.
- Van Cauwenberge P, Bachert C, Passalacqua G et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. *Allergy* 2000;**55**:116–134.
- Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CEH, Greaves MW, Henz BM et al. EAACI/GA²LEN/EDF guideline: management of urticaria. *Allergy* 2006;**61**:321–331.
- Monroe E. Review of H₁ antihistamines in the treatment of chronic idiopathic urticaria. *Cutis* 2005;**76**:118–126.
- Gregory C, Cifaldi M, Tanner LA. Targeted intervention programs: creating a customized practice model to improve the treatment of allergic rhinitis in a managed care population. *Am J Manag Care* 1999;**5**:485–496.
- Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic asthma in Europe. *Eur Respir J* 2004;**24**:758–764.
- Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;**99**(6 Suppl. 2):S808–S814.
- Foley S, Hamid Q. Inflammatory patterns in allergic rhinitis. *Clin Exp Allergy Rev* 2006;**6**:91–95.
- Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001;**108**(Suppl. B):S2–S8.
- Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol* 1997;**99**(Suppl.):S773–S780.
- Grossmann J. One airway, one disease. *Chest* 1997;**111**(Suppl. 2):11S–16S.
- O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997;**136**:197–201.
- Greaves MW. Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol* 2003;**3**:363–368.
- Grattan CEH. Towards rationalizing the nomenclature and classification of urticaria: some guidance on guidelines. *Clin Exp Allergy* 2007;**37**:625–626.
- Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CEH, Greaves MW, Henz BM et al. EAACI/GA²LEN guideline definition, classification and diagnosis of urticaria. *Allergy* 2006;**61**:316–320.
- Negro-Alvarez JM, Miraller-López JC. Chronic idiopathic urticaria treatment. *Allergol Immunopathol* 2001;**29**:129–132.
- Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. *Drugs* 2004;**64**:2515–2536.
- Garcia-Rafanell J. Rupatadine fumarate: antiallergic, histamine and PAF antagonist. *Drugs Fut* 1996;**21**:1033–1036.
- Van Den Anker-Rakhmanina NY. Rupatadine. *Curr Opin Anti-inflamm Immunomodul Invest Drugs* 2000;**2**:127–132.
- Izquierdo I, Merlos M, Garcia-Rafanell J. Rupatadine, a new selective histamine H₁ receptor and platelet-activating factor (PAF) antagonist: a review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today (Barc)* 2003;**39**:451–468.

29. Picado C. Rupatadine: pharmacological profile and its use in the treatment of allergic disorders. *Expert Opin Pharmacother* 2006;**7**:1989–2001.
30. Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007;**67**:457–474.
31. Howarth PH, Salagean M, Dokic D. Allergic rhinitis: not purely a histamine-related disease. *Allergy* 2000;**55**:7–16.
32. Quraishi SA, Davies MJ, Craig TJ. Inflammatory responses in allergic rhinitis: traditional approaches and novel treatment strategies. *J Am Osteopathol Assoc* 2004;**104**(Suppl. 5):S7–S15.
33. Pearlman DS. Pathophysiology of the inflammatory response. *J Allergy Clin Immunol* 1999;**104**:S132–S137.
34. Bascom R, Pipkorn U, Proud D, Dunette S, Gleich GJ, Lichtenstein LM et al. Major basic protein and eosinophils-derived neurotoxin concentrations in nasal-lavage fluid after antigen challenge: effect of systemic corticosteroids and relationship to eosinophil influx. *J Allergy Clin Immunol* 1989;**84**:338–346.
35. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late-phase response to antigen challenge. Effect of systemic steroid pretreatment. *Am Rev Respir Dis* 1988;**138**:406–412.
36. Horak F. Clinical advantages of dual activity in allergic rhinitis. *Allergy* 2000;**55**(Suppl. 64):34–39.
37. Merlos M, Giral M, Balsa D, Ferrando R, Queralt M, Puigdemont A et al. Rupatadine, a new potent, orally active dual antagonist of histamine and platelet-activating factor (PAF). *J Pharmacol Exp Ther* 1997;**280**:114–121.
38. Barrón S, Ramis I, Garcia-Rafanell J, Merlos M. Inhibitory activity of rupatadine on pro-inflammatory cytokine production, relationship with binding affinity. *Methods Find Exp Clin Pharmacol* 2005;**27**(Suppl. 2):161–162.
39. Giral M, Balsa D, Ferrando R, Merlos M, Garcia-Rafanell J, Forn J. CNS activity profile of rupatadine fumarate, a new dual receptor antagonist of platelet-activating factor (PAF) and histamine. *Allergy* 1998;**53**(Suppl.):131.
40. Merlos M, Balsa D, Giral M, Ferrando R, Garcia-Rafanell J, Forn J. Inhibition of rat peritoneal mast cell exocytosis by rupatadine fumarate: a study with different secretagogues. *Methods Find Exp Clin Pharmacol* 1997;**19**(Suppl. A):148.
41. Merlos M, Ferrando R, Giral M, Ramis I, Forn J. Effect of topical rupatadine on experimental conjunctivitis in guinea pigs: macroscopic evaluation of ocular lesions. *J Allergy Clin Immunol* 2001;**107**(Suppl. 2):S310.
42. Queralt M, Merlos M, Giral M, Puigdemont A. Dual effect of a new compound, rupatadine, on edema induced by platelet-activating factor and histamine in dogs: comparison with antihistamines and PAF antagonists. *Drug Dev Res* 1996;**39**:12–18.
43. Queralt M, Brazis P, Merlos M, Puigdemont A. Inhibitory effects of rupatadine on mast cell histamine release and skin wheal development induced by *Ascaris suum* in hypersensitive dogs. *Drug Dev Res* 1998;**44**:49–55.
44. Queralt M, Brazis P, Merlos M, de Mora F, Puigdemont A. In vitro inhibitory effect of rupatadine on histamine and TNF- α release from dispersed canine skin mast cells and the human mast cell line HMC-I. *Inflamm Res* 2000;**49**:355–360.
45. Ferrando R, Giral M, Balsa D, Merlos M, Garcia-Rafanell J, Forn J. Protective effect of rupatadine fumarate in experimental conjunctivitis in guinea pigs. *Methods Find Exp Clin Pharmacol* 1996;**18**(Suppl. B):140.
46. Stuebner P, Horak F, Zieglmayer R, Arnáiz E, Leuratti C, Peréz I et al. Effects of rupatadine vs placebo on allergen-induced symptoms in patients exposed to aeroallergens in the Vienna Challenge Chamber. *Ann Allergy Asthma Immunol* 2006;**96**:37–44.
47. Izquierdo I, Nieto C, Ramis J, Cooper M, Dewland P, Forn J. Pharmacokinetics and dose linearity of rupatadine fumarate in healthy volunteers. *Methods Find Exp Clin Pharmacol* 1997;**19**(Suppl. A):189–203.
48. Barbanj MJ, García-Gea C, Morte A, Izquierdo I, Pérez I, Jané F. Central and peripheral evaluation of rupatadine, a new antihistamine/platelet-activating factor antagonist, at different doses in healthy volunteers. *Neuropsychobiology* 2004;**50**:311–321.
49. Curtin ML. Current status of platelet-activating factor antagonists. *Exp Opin Ther Patents* 1998;**8**:703–711.
50. Marques SA, Dy LC, Southall MD, Yi Q, Smietana E, Kapur R et al. The platelet-activating factor receptor activates the extracellular signal-regulated kinase mitogen-activated protein kinase and induces proliferation of epidermal cells through an epidermal growth factor-receptor-dependent pathway. *J Pharmacol Exp Ther* 2002;**300**:1026–1035.
51. Merlos M, Ramis I, Balsa D, Queralt M, Brazis P, Puigdemont A. Inhibitory effect of rupatadine on TNF- α release from human monocytes and mast cell line HMC-1. *J Allergy Clin Immunol* 2000;**105**(Suppl. 1):S62.
52. Barrón S, Ramis I, Merlos M. Rupatadine inhibits the inflammatory component of allergic response: cytokine release, adhesion molecule expression and inflammatory cell recruitment. 23rd EAACI Congress, 12–16 June 2004, Amsterdam.
53. Merlos M, Giral M, Balsa D, Ferrando R, Garcia-Rafanell J, Forn J. Rupatadine inhibits the eosinophil recruitment in BAL fluid of ovalbumin-sensitized guinea pigs. *J Allergy Clin Immunol* 1998;**101**(Suppl. 1):S218.
54. Ramis I, Giral M, Ferrando R, Merlos M. Inhibition of PAF- and LTB₄-induced human neutrophil chemotaxis by rupatadine using a new fluorescent chemotaxis assay. *Allergy* 2000;**55**(Suppl. 63):94–95.
55. Barrón S, Roman J, Michelena P, Ramis I, Merlos M. Rupatadine inhibits cytokine production and NF- κ B activity by histamine H₁ receptor-dependent mechanism. *Rev Rinol* 2006;**6**:18.
56. Barrón S, Ramis I, Merlos M. Effect of rupatadine on lymphocyte cytokine production. *Allergy Clin Immunol Int* 2005;**1**(Suppl. 1):427.
57. Scannell RT, Differding E, Talaga P. Dual acting antihistaminergic agents. *Mini Rev Med Chem* 2004;**4**:923–933.
58. Roumestan C, Henriquet C, Mathieu M, Bousquet J. Effects of rupatadine on inflammatory mediators and transcription factors: a comparison with desloratadine and levocetirizine. *Allergy Clin Immunol Int* 2005;(Suppl. 1):450.
59. Mion O, Mello Jr J, Castro F, Cruz A, Mocelin M, Bogart P et al. Rupatadine fumarate is effective in the treatment of persistent allergic rhinitis: a multicentre study. *Allergy* 2007;**62**(Suppl. 83):137.
60. Izquierdo I, Paredes I, Lurigados C, Sospedra E, Cooper M, Thomas H. A dose ranging study of rupatadine fumarate in patients with seasonal allergic rhinitis. *Allergy* 2000;**55**(Suppl. 63):275.
61. Pérez I, De la Cruz G, Villa M, Izquierdo I. Rupatadine in allergic rhinitis: pooled analysis of efficacy data. *Allergy* 2002;**57**(Suppl. 73):245.
62. Saint-Martin F, Dumur JP, Pérez I, Izquierdo I. A randomized, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine (20 and 10 mg), a new PAF and H₁ receptor-specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis. *J Investig Allergol Clin Immunol* 2004;**14**:34–40.

63. Martínez-Cócerca C, De Molina M, Martí-Guadaño E, Pola J, Conde J, Borja J et al. Rupatadine 10 mg and cetirizine 10 mg in seasonal allergic rhinitis: a randomised, double-blind parallel study. *J Invest Allergol Clin Immunol* 2005;**15**:22–29.
64. Guadaño EM, Serra-Batlles J, Meseguer J, Castillo JA, de Molina M, Valero A et al. Rupatadine 10 mg and ebastine 10 mg in seasonal allergic rhinitis: a comparison study. *Allergy* 2004;**59**:766–771.
65. Valero A, Bartra J, Serrano C, Donado E, García O, Izquierdo I et al. Rupatadine reduces nasal obstruction in allergen-induced rhinitis. *Allergy* 2007;**62**(Suppl. 83):137–138.
66. Roger A, Arnáiz E, Valero A, De la Torre F, Castillo JA, Rivas P et al. Rupatadine 10 mg improves quality of life in long-term treatment of persistent allergic rhinitis [abstract no. 761 plus poster]. 25th EAACI Congress 10–14 June 2006, Vienna.
67. Fantin S, Maspero J, Bisbal C, Agache I, Donado E, García O et al. A 12-week placebo-controlled study of rupatadine 10 mg once daily comparative with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. In press, *Allergy*, 2008.
68. Gimenez-Arnau A, Pujol RM, Ianosí S, Kaszuba A, Malbran A, Poop G et al. Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicenter study. *Allergy* 2007;**62**:539–546.
69. Dubertret L, Zalupeca 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**:223–228.
70. Gimenez-Arnau A, Donado E, Arnaiz E, Perez I, Izquierdo I. Fast onset of action of rupatadine in the reduction of pruritus in patients suffering from chronic urticaria: pooled analysis. *Allergy* 2007;**62**(Suppl. 83):306.
71. Gimenez-Arnau A, Perez I, Donado E, Pujol-Vallverdú RM, Arnaiz E, Izquierdo I. The use of a responder analysis to identify clinical meaningful differences in patients suffering from chronic urticaria following a 4-weeks treatment with rupatadine 10- and 20 mg. World Congress of Dermatology, 1–5 October 2007, Buenos Aires.
72. Juniper EF. Can quality of life be quantified? *Clin Exp All Rev* 2002;**2**:57–60.
73. Solans A, Merlos M, Antonijoan R, Barbanoj M, Donado E, Izquierdo I et al. Pharmacokinetic and safety profile of rupatadine when coadministered with azithromycin: a randomized, crossover, multiple-dose open study. *Allergy Clin Immunol Int* 2005;(Suppl. 1):159.
74. Solans A, Carbó M, Peña J, Nadal T, Izquierdo I, Merlos M. Influence of food on the oral bioavailability of rupatadine tablets in healthy volunteers: a single-dose, randomized, open-label, two-way crossover study. *Clin Therap* 2007;**29**:900–908.
75. Barbanoj MJ, García-Gea C, Antonijoan R et al. Evaluation of the cognitive, psychomotor and pharmacokinetic profiles of rupatadine, hydroxyzine and cetirizine, in combination with alcohol, in healthy volunteers. *Hum Psychopharmacol Clin Exp* 2006;**21**:13–26.
76. Efficacy Guideline. El: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. ICH Harmonised Tripartate Guideline, 1995. Available at: <http://www.ich.org> (accessed January 2008).
77. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on the clinical development of medicinal products for the treatment of allergic rhinoconjunctivitis. Available at: <http://www.emea.europa.eu> (accessed January 2008).
78. Valero A, Rivas P, Castillo JA, Borja J, Donado E, Arnaiz E et al. One year safety data of rupatadine 10 mg in patients with allergic rhinitis. 25th EAACI Congress 10–14 June, 2006, Vienna.
79. Gimenez-Arnau A, Pujol R, Donado E, Arnaiz E, Perez I, Izquierdo I. Safety profile of rupatadine in the treatment of chronic urticaria. *Allergy* 2007;**62**(Suppl. 83):306.
80. Hove-Madsen L, Llach A, Molina CE, Prat-Vidal C, Farré J, Roura S et al. The proarrhythmic antihistaminic drug terfenadine increases spontaneous calcium release in human atrial myocytes. *Eur J Pharmacol* 2006;**553**:215–221.
81. Dávila I, Sastre J, Bartra J, del Cuvillo A, Jáuregui I, Montoro J et al. Effect of H₁ antihistamines upon the cardiovascular system. *J Invest Allergol Clin Immunol* 2006;**16**(Suppl. 1):13–23.
82. Donado E, García O, Pérez I, Barbanoj M, Antonijoan R, Peña J et al. Cardiac safety of rupatadine according to the new ICH guideline: a “thorough QT/QTc study” [abstract no. 760 plus poster]. 25th EAACI Congress 10–14 June, 2006, Vienna.
83. Izquierdo I, Pérez I, Villa M, Giral M, Merlos M, Forn J. Lack of electrocardiographic effects of rupatadine, new non-sedating selective histamine H₁-receptor and PAF antagonist. *Allergy* 2001;**56**(Suppl. 68):212.
84. Giral M, Merlos M, Balsa D, Ferrando R, Garcia-Rafanell J, Forn J. Effects of rupatadine on cardiovascular profile in rats and guinea pigs: comparison with other non-sedating antihistamines. *Allergy* 1997;**52**(Suppl. 37):44–45.
85. Ramis I, Giral M, Nieto C, Martel E, Merlos M. Lack of cardiotoxic effects of rupatadine in isolated Purkinje fibres and its relationship with rupatadine cardiac levels. *Allergy* 2000;**55**(Suppl. 63):264.
86. Caballero R, Valenzuela C, Longobardo M, Tamargo J, Delpón E. Effects of rupatadine, a new dual antagonist of histamine and platelet-activating factor receptors, on human cardiac Kv1.5 channels. *Br J Pharmacol* 1999;**128**:1071–1081.
87. Antonijoan R, Garcia-Gea C, Ballester M, Donado E, Perez I, Blanch I et al. Rupatadine not potentiate the depressant CNS effects of benzodiazepines. *Allergy* 2007;**62**(Suppl. 83):490.
88. Vuurman E, Theunissen E, van Oers A, van Leeuwen C, Jolles J. Lack of effects between rupatadine 10 mg and placebo on actual driving performance of healthy volunteers. *Human Psychopharmacol Clin Exp* 2007;**22**:289–297.
89. Bousquet J. Is the impairment of quality of life acceptable for the patient? *Clin Exp All Rev* 2002;**2**:61–65.
90. Bachert C. Quality of life: improvement due to treatment. *Clin Exp All Rev* 2002;**2**:73–78.
91. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;**9**:210–216.
92. Tillement J-P. Pharmacological profile of the new antihistamines. *Clin Exp All Rev* 2005;**5**:7–11.
93. Walsh GM. Anti-inflammatory properties of antihistamines: an update. *Clin Exp All Rev* 2005;**5**:21–25.
94. Devillier P. Comparing the new antihistamines: the role of pharmacological parameters. *Clin Exp Allergy* 2006;**36**:5–7.

Appendix

Levels of scientific best evidence as applied to data from clinical studies (adapted from Clark W, Mucklow J. Gathering and weighing the evidence. In: Panton R, Chapman S (eds). Medicines Management. London BMJ Books and Pharmaceutical Press; 1998.

Level 1: Strong evidence from at least one systematic review.

Level 2: Evidence from randomized controlled clinical trials.

Level 3: Evidence from well-designed trials without randomization, single-group pre/postintervention, cohort, time series, or matched case control studies.

Level 4: Evidence from well-designed nonexperimental observational studies from more than one centre or research group.

Level 5: Opinions of respected authorities based on clinical experience, descriptive studies, and reports of Expert Committees.
