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ALLERGY

Original article

The ARIA/EAACI criteria for antihistamines: an assessment of the efficacy, safety and pharmacology of desloratadine

Background: The definition of allergic rhinitis and the classification of its severity and treatment have advanced in recent years following the publication of the Allergic Rhinitis and its Impact of Asthma (ARIA) document. The ARIA and the European Academy of Allergology and Clinical Immunology (ARIA/EAACI) have published a set of recommendations that outline the pharmacological and clinical criteria to be met by medications commonly used in the treatment of allergic rhinitis.
Methods: An international group of experts met to assess the profile of the antihistamine, desloratadine, under the ARIA/EAACI criteria. Data on desloratadine were collected from peer-reviewed clinical studies and review articles, which were corroborated and augmented by comprehensive public access documents from the European Medicines Evaluation Agency (EMEA).
Results and conclusion: Based on this systematic review, it was concluded that the efficacy, safety and pharmacology of desloratadine broadly meet the ARIA/EAACI criteria for antihistamines.

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Key words: antihistamine, allergy, ARIA, desloratadine, guidelines, rhinitis, therapy

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The definition and classification of allergic rhinitis underwent a significant change in 2001 following the publication of the Allergic Rhinitis and its Impact on Asthma (ARIA) document (1). The ARIA, an initiative in collaboration with the World Health Organization (WHO), reaffirms allergic rhinitis as a major chronic respiratory disease with important co-morbidities, including asthma, for which allergic rhinitis is a risk factor. Under ARIA, allergic rhinitis has been reclassified according to the chronicity of symptoms (intermittent/persistent) and its relative severity based on symptoms and quality of life (mild, moderate or severe). Arising from this disease classification, a stepwise approach to the treatment of allergic rhinitis is recommended by ARIA, which includes the use of second-generation antihistamines and topical nasal corticosteroids. More recently, the European Academy of Allergology and Clinical Immunology (EAACI) collaborated with ARIA to define a framework of requirements for the pharmacology, efficacy and safety of antihistamines and nasal corticosteroids (2). Furthermore, the ARIA/EAACI document outlined the basis for determining the clinical efficacy of antihistamines in terms of symptom control, rather than the use of simulated models. While the ARIA/EAACI requirements note that no third-generation antihistamine exists, the criteria highlighted in the document (Table 1) provide an appropriate basis for systematically reviewing the efficacy, safety and pharmacology of existing antihistamines. The Desloratadine Allergy Advisory Group met to discuss the overall profile of desloratadine in terms of the ARIA/EAACI requirements document.

Table 1. The Allergic Rhinitis and its Impact of Asthma (ARIA)-European Academy of Allergology and Clinical Immunology (EAACI) requirements for antihistamines. Adapted from (2).

Pharmacologic properties
Potent and selective H1 receptor blockade
Additive anti-allergic activities
It is proposed to ascribe 'anti-allergic effects' to oral H_1-antihistamines possessing the following properties:
Any claim for additive anti-allergic properties should be linked to a clinical benefit for the patient for the treatment of allergic symptoms (e.g. corticosteroid sparing effect in asthma)
A mechanistic explanation of the anti-allergic effect should be added
–reduction in the levels of pro-inflammatory mediators, adhesion molecules or cytokines in nasal or ocular secretions,
–and/or reduction in the number of inflammatory cells in the skin, nasal or ocular tissues
–During challenge or natural allergen exposure (i.e. pollen season, natural mite exposure)
–At the recommended dose.
–Assessment of anti-allergic properties for combinations (with decongestants or anti-leukotrienes)
No clinically relevant pharmacokinetic interference by foods, medications or intestinal transport proteins
No known interaction with cytochrome P4503A (CYP3A)
No known interaction with disease to avoid toxic reactions
Efficacy
Effective in the treatment of intermittent and persistent rhinitis as defined in the ARIA document
Effective for all nasal symptoms including nasal obstruction
Improvement of eye symptoms
If a claim for asthma is made
Improvement of asthma symptoms (short term studies)
Reduction of asthma exacerbations (long term studies)
An improvement of the pulmonary function tests, although in pollen-induced bronchial symptoms, FEV_1 and peak flow rates are usually not altered.
If a claim for a preventive effect is proposed, appropriate trials should be conducted
Studies should be carried out in young children and elderly patients to assess efficacy
Side effects
No sedation or cognitive or psychomotor impairment
No anti-cholinergic effects
No weight gain
No cardiac side effects
Possible use in pregnancy and breast feeding
Studies should be carried out in young children and elderly age patients to assess safety
Prospective postmarketing safety analyses should be conducted
Pharmacodynamics
Rapid onset of action
Long duration of action, at least persistence of clinical effects at the end of the 24-h dosing period, so the drug can be administered once a day
No likelihood of development of tolerance (tachyphylaxis)
Comparison with other drugs used to treat rhinitis (conjunctivitis)

Methods

The Desloratadine Allergy Advisory Group consisted of experts in the fields of allergy, otorhinolaryngology, pulmonology and dermatology. The database of studies was collected from electronic databases, including Medline, EMBASE, Current Contents and SciSearch. The search strategy was designed to identify peer-reviewed clinical studies and relevant review articles. Full-text articles were retrieved and hand-searched for relevant information related to the ARIA/EAACI requirements for antihistamines. Data were extracted, summarized, and discussed under the headings of pharmacokinetics (including anti-allergic effects), efficacy, safety and pharmacodynamics. Efficacy assessments made during this review were based on data from placebo-controlled clinical trials of desloratadine. Data from artificial models, such as, nasal airflow studies in allergen exposure units were assessed only to support findings already obtained in placebo-controlled clinical trials (e.g. reductions in nasal congestion). Histamine-induced wheal and flare studies were not assessed, as the ARIA/EAACI guidelines previously noted that this type of study does not predict clinical efficacy in allergic rhinitis (2). A further source of independent corroboratory information was the European Medicine Evaluation Agency (EMEA) European Public Assessment Report (EPAR) publications (3). The EPAR summarizes the scientific information on what was considered by the Committee for Proprietary Medicinal Products (CPMP) for the centralized approval of desloratadine in the European Union. The EPAR therefore contains an independent and exhaustive review of the pharmacology, efficacy and safety of desloratadine. The EPAR was used to corroborate information from review articles that were not contained in individual peer-reviewed literature and was also used to address specific pharmacokinetic/safety criteria.

Pharmacologic properties

Potent and selective H_1 receptor antagonism

The potency and selectivity profile of desloratadine has been studied extensively in a wide variety of cellular and animal models. The most relevant data on the interaction of desloratadine with the histamine H_1 receptor comes from work performed with recombinant cloned human H_1 receptors expressed in Chinese hamster ovary cells (4). Desloratadine is a potent antagonist at the human H_1 receptor, with specific, saturatable high-affinity binding having been demonstrated. In competitive binding studies using radiolabeled pyrilamine, desloratadine had an affinity constant (K_i) of 0.9 nM. These results are in agreement with data from animal models showing the high affinity of desloratadine for the H_1 receptor (5).

Desloratadine demonstrates relative selectivity for the H_1 receptor over other receptor populations, such as H_2 receptors and muscarinic receptors (5). The affinity of desloratadine for human muscarinic receptors is approximately 50–350 times less than its affinity for the H_1 receptor (4, 5) (Table 2). Studies in rabbit and guinea pig eye models do not demonstrate any relevant anticholinergic activity for desloratadine, as only high concentrations (10^{-6} M) of topically administered desloratadine were used (6). Desloratadine is at least 60 times more selective for H_1 receptors than H_2 receptors. Desloratadine had no activity in a wide range of over 100 other receptor families, including dopamine, monoamine oxidase, bradykinin, and GABA-ergic receptors (5).

Additive anti-allergic activities

Numerous studies have been undertaken into the potential anti-allergic effects of antihistamines (7–9). Most groups have studied the effects of relatively high concentrations of antihistamines on the release of mediators from leukocytes (mast cells, basophils) or harvested mucosal/smooth muscle cells *in vitro*. For the purposes of this review, only *in vitro* studies of desloratadine that employed concentrations approximating those seen following oral dosing were assessed.

In human umbilical vein endothelial cells, desloratadine inhibited histamine-induced expression of the adhesion molecule, P-selectin (10). This inhibition occurred at a low concentration of desloratadine, with an IC_{50} of 23×10^{-9} M. Similarly, the IC_{50} values for the inhibition by desloratadine of histamine-induced interleukin (IL)-6 and IL-8 occurred at low concentrations of 2.6×10^{-12} and 1×10^{-9} M, respectively (Fig. 1). Another study demonstrated that desloratadine at a concentration of 10^{-9} M had an inhibitory effect on the release of IL-3, IL-6, IL-8, tumor necrosis factor-α (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) from human mast cells and basophils (11). The magnitude of this inhibition was comparable with or larger than that seen with 10^{-8} M dexamethasone (Table 3).

Table 2. The affinities of desloratadine for human H_1 and guinea pig H_2 histaminic receptors and human M_1, M_2, M_4 and M_5 muscarinic receptors *in vitro*. Human H_1 receptor data from Anthes et al. (4); guinea pig H_2 and human muscarinic data from Kreutner et al. (5)

Receptor	Source	Affinity (Ki, nM)
Histamine H_1	Human recombinant	0.9
Histamine H_2	Guinea pig striatum	353
Muscarinic M_1	Human recombinant	50
Muscarinic M_2	Human recombinant	47
Muscarinic M_4	Human recombinant	104
Muscarinic M_5	Human recombinant	320

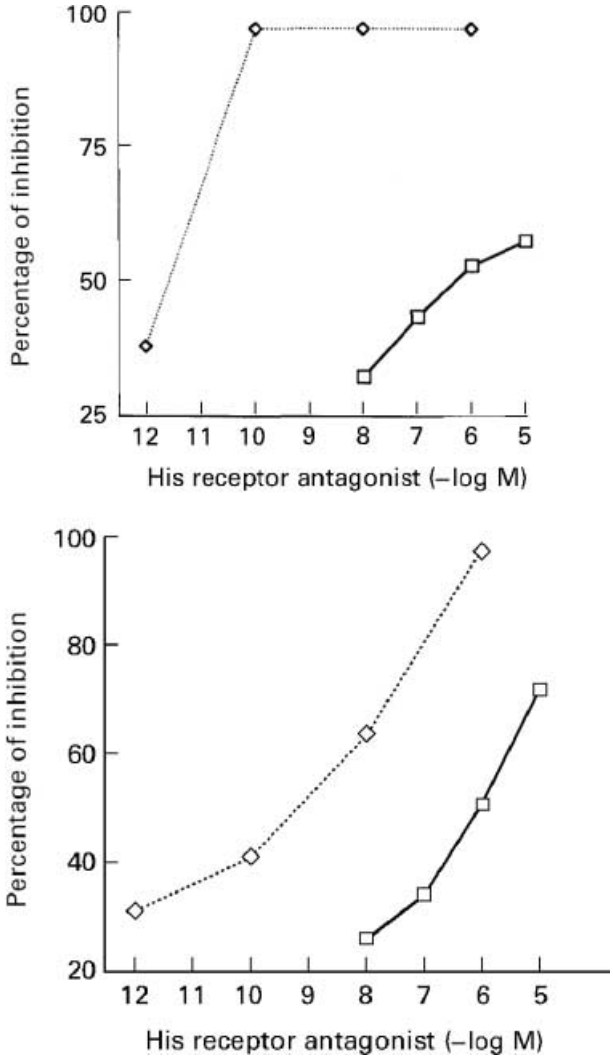

Figure 1. Percentage inhibition of the release of interleukin (IL)-6 (upper panel) and IL-8 (lower panel) from human umbilical vein endothelial cells *in vitro* by the histamine (His) receptor antagonists, desloratadine (◇) and loratadine (□). The positive control was the release of IL-6 or IL-8 induced by histamine (10^{-4} M). Reproduced from Molet et al. (10), *Clinical and Experimental Allergy* 1997, with the permission of Blackwell Publishing Ltd.

Table 3. Percentage inhibition of cytokine release from HMC-1 mast cells following preincubation with desloratadine, cetirizine, ranitidine and dexamethasone for 1 h, followed by a 24-h coincubation with PMA and calcium ionophore. Data are expressed as means (±SD) of at least four experiments. Adapted from Lippert et al. (11) Experimental Dermatology 2000, with the permission of Blackwell Publishing Ltd.

	IL-6	IL-8	TNF-α	IL-3	GM-CSF
Desloratadine, 10^{-9} M	32.6 ± 9.1	32.6 ± 10.7	64.5 ± 18.3	32.1 ± 12.3	27.8 ± 18.2
Cetirizine, 10^{-9} M	8.0 ± 1.8	23.0 ± 9.3	29.0 ± 12.3	17.8 ± 7.8	6.2 ± 2.6
Ranitidine, 10^{-8} M	10.0 ± 2.1	6.8 ± 3.2	33.0 ± 6.6	18.5 ± 3.8	12.4 ± 2.7
Dexamethasone, 10^{-8} M	32.0 ± 7.3	46.0 ± 12.8	54.0 ± 18.1	14.4 ± 4.4	31.0 ± 20.3

IL, interleukin; TNF-α, tumor necrosis factor-α; GM-CSF, granulocyte-macrophage colony-stimulating factor; AUC, area under the curve.

The mechanism by which desloratadine achieves these *in vitro* anti-allergic effects has not been delineated fully. However, H_1 receptors are now known to exhibit constitutive activity in the absence of bound agonist (histamine) (12). This constitutive activity stimulates the activation of the intracellular inflammatory regulatory entity, nuclear factor κB (NF-κB), which in turn promotes the expression of inflammatory cytokines. Antihistamines act as inverse agonists at the H_1 receptor to downregulate both basal and histamine-stimulated NF-κB activity (13). While the clinical correlate of this mechanism has yet to be established, preliminary evidence does suggest a modulatory role for desloratadine at the level of NF-κB (14).

Studies of the anti-allergic profile of desloratadine in the clinical setting remain to be performed. As noted in the ARIA/EAACI guidelines, such studies should demonstrate a clinical benefit for the patient in terms of reduced allergic symptoms, reduced levels of inflammatory mediators in nasal/ocular secretions, and/or reduced inflammatory cells in skin, nasal or ocular secretions. Before ascribing a clinically relevant anti-allergic effect, such effects should be seen during allergen exposure (natural or experimental) and at the clinically recommended dose. Anti-allergic effects of antihistamines in combination with other medications should also be studied.

No clinically relevant pharmacokinetic interference by foods, medications or intestinal transport proteins

The absorption of desloratadine in the presence and absence of food was studied by Gupta et al. in 18 healthy volunteers (15). Subjects received a single dose of desloratadine 7.5 mg orally after a 10-h fast or after a high-calorie, high-fat meal (immediately after a 10-h fast), and blood samples were taken to assay desloratadine pharmacokinetics. There was no significant difference in desloratadine pharmacokinetics between the fasted and fed groups (Fig. 2). The fasted to fed ratios for the maximum plasma concentration (C_{max}) and area under the curve (AUC_{0-24}) for desloratadine were 108 and 101%, respectively.

The drug–drug interaction profile of desloratadine has been studied with a wide range of important medications.

In an *in vitro* study using human liver microsomes, desloratadine did not inhibit cytochrome P450 (CYP) subtypes CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 at concentrations many times higher than those achieved following oral dosing in humans (16). Of note, the principal 3-hydroxy metabolite of desloratadine also had little or no effect on the functioning of these CYP enzymes even at very elevated concentrations.

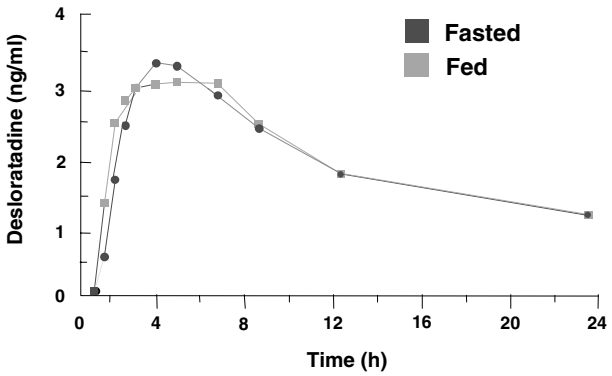

Figure 2. Lack of effect of food on the bioavailability of desloratadine. Healthy subjects received a single dose of desloratadine 7.5 mg after a 10-h fast (fasted) or after a high-calorie, high fat meal, immediately preceded by a 10-h fast (fed). Reproduced from Gupta et al. (15), *Clinical Pharmacokinetics* 2002, with the permission of ADIS Publishing Ltd.

Drug–drug interaction studies have also been performed in humans following oral dosing with desloratadine (Table 4):

- Banfield et al demonstrated that following co-administration of desloratadine 7.5 mg once daily (QD) and the CYP3A4 inhibitor erythromycin 500 mg three times a day (TID) for 10 days in 24 healthy subjects, no clinically or statistically significant changes were noted in electrocardiographic (ECG) parameters (17). The C_{max} and the AUC_{0-24} were slightly higher (20 and 10%, respectively) during co-administration with erythromycin compared with desloratadine administration alone.

Table 4. The effects of coadministration with cytochrome P450 inhibitors on the pharmacological exposure to desloratadine

	Coadministered compound				
	Ketoconazole	Cimetidine	Erythromycin	Azithromycin	Fluoxetine
Desloratadine	AUC 39%↑	AUC 19%↑	AUC 10%↑	AUC 5%↑	AUC unaffected

AUC, area under the curve.

- When desloratadine 5 mg QD was co-administered with azithromycin (500 mg, then 250 mg QD) for 4 days in healthy volunteers, only minor alterations in C_{max} (15% increase) and AUC_{0-24} (5% increase) were seen (18). The ECG profiles of subjects were unchanged during desloratadine–azithromycin co-administration.
- The pharmacokinetics of desloratadine 7.5 mg QD and ketoconazole 200 mg twice daily (BD) for 10 days were studied in 24 healthy volunteers (19). The AUC_{0-24} for desloratadine rose by 39%, while the C_{max} for desloratadine only rose by 45% during co-administration, which were clinically non-relevant changes. Co-administration of desloratadine and ketoconazole had no impact on ECG parameters during the study.
- In a study involving 36 healthy subjects, desloratadine 5 mg QD and cimetidine 600 mg BD were co-administered for 14 days (3). Compared with desloratadine administered alone, the combination of desloratadine and cimetidine was associated with minor increases in the C_{max} (12%) and AUC_{0-24} (19%) for desloratadine.
- Subjects ($n = 54$) receiving either desloratadine 5 mg QD alone or in combination with fluoxetine (20 mg QD) demonstrated that the combination of fluoxetine and desloratadine for 7 days did not alter the pharmacokinetics of desloratadine to a relevant degree (3). The C_{max} and AUC_{0-24} for desloratadine rose by 15 and 0%, respectively following co-administration with fluoxetine.

Two major transport systems, P-glycoprotein (P-gp) and the organic anion transport polypeptide (OATP) have been found to play an important role in the intestinal absorption and distribution of antihistamines (20, 21) Modulation of the activity of P-gp and OATP can alter the bioavailability of antihistamines. Citrus juices, particularly grapefruit juice, have been shown to affect the absorption of some antihistamines via actions at the level of P-gp, OATP or both (22).

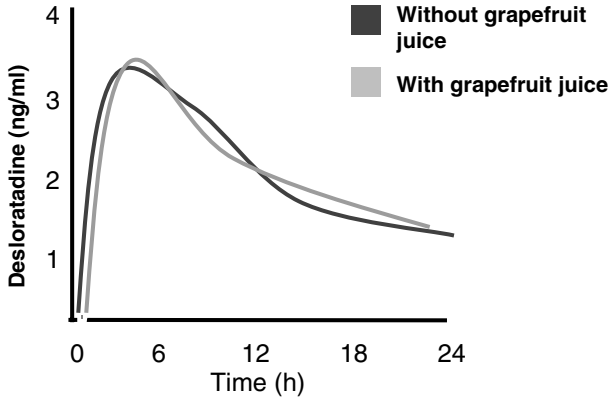

Figure 3. Lack of effect of dosing with grapefruit juice on the bioavailability of desloratadine. Healthy subjects consumed grapefruit juice three times daily for 2 days prior to receiving a single dose of desloratadine 5 mg, and further grapefruit juice was taken with desloratadine and 2-h postdosing. Adapted from Banfield et al. (23), *Clinical Pharmacokinetics* 2002, with the permission of ADIS Publishing Ltd.

Twenty-four healthy volunteers received a single dose of desloratadine 5 mg QD taken with or without grapefruit juice TID for 2 days before desloratadine was administered (23). Further grapefruit juice was taken at the time of desloratadine dosing and 2 h later. The C_{max} and AUC of desloratadine were unaffected by grapefruit juice (Fig. 3). Further evidence of the lack of interaction of desloratadine with P-gp was reported by Wang et al. using cells that expressed P-gp *in vitro* (24). The concentration of desloratadine that was required to produce 50% inhibition of P-gp was approximately 880 times the C_{max} seen in humans following ingestion of 5 mg of desloratadine.

No known interaction with cytochrome P4503A (CYP3A)

Interaction studies between desloratadine and compounds known to influence CYP 3A4 have shown no significant impact on the function of the 3A4 isoenzyme. As noted above, neither ketoconazole 200 mg BD nor erythromycin 500 mg TID for 10 days led to sizeable or clinically relevant changes in desloratadine pharmacokinetics (17, 19), indicating that desloratadine has no clinically relevant inhibitory effect on CYP3A4.

No known interaction with disease to avoid toxic reactions

Affrime et al. studied the pharmacokinetic profile of desloratadine 5 mg for 10 days in a large diverse group of healthy subjects (25). Following stratification of subjects by age (3 groups: 19–45 years, 46–64 years, 65–70 years), no relevant differences existed among the groups in terms of pharmacokinetic parameters. No dose adjustment is required in elderly patients.

In patients with hepatic impairment treated with a single dose of desloratadine 7.5 mg, the C_{max} and AUC of desloratadine were increased 2.4- and 2.3-fold, respectively, and was safe and well tolerated (3). In a multiple dose study of desloratadine 5 mg QD for 10 days in patients with moderate hepatic impairment had an AUC_{0-24} for desloratadine that was threefold higher than in normal volunteers (3). As the increased desloratadine exposure was well tolerated no dose adjustment in hepatic disease is recommended.

In patients with chronic renal impairment, a 1.5- to 2.5-fold increase in desloratadine AUC_{0-24} and C_{max} was seen, and labeling recommends that patients with severe renal impairment use desloratadine with caution (3). However, desloratadine is not contraindicated in patients with renal impairment.

Pharmacologic properties

- Desloratadine is a potent and selective H_1-receptor antagonist.
- Studies have shown no clinically relevant interference with the pharmacology of desloratadine by foods, medications or intestinal transport proteins.
- Co-administration studies with desloratadine have demonstrated no relevant interaction with cytochrome P4503A (CYP3A).
- A dose reduction may be necessary in patients with severe renal failure receiving desloratadine, however, no known interactions with diseases have been demonstrated to cause toxic reactions.

Efficacy

Effective in the treatment of intermittent and persistent rhinitis as defined in the ARIA document

The ARIA definition of intermittent rhinitis requires symptoms to be present for <4 days per week or <4 weeks per year (1). Persistent rhinitis is defined in the ARIA document as requiring symptoms to be present for more than 4 days per week and for more than four consecutive weeks per year. The database reviewed did not contain studies of desloratadine performed strictly under the ARIA classification. The terms *seasonal* and *intermittent* and *perennial* and *persistent* are not interchangeable (26). Therefore, existing studies of desloratadine in seasonal and perennial rhinitis were re-examined to assess whether the characteristics of allergic rhinitis of patients enrolled in these studies met the ARIA classifications. This methodological assessment focused on the duration of symptoms at enrolment/screening, and the presence of symptoms throughout the duration of the study in placebo- and desloratadine-treated groups.

Intermittent rhinitis. Patients with intermittent rhinitis suffer from symptoms for relatively brief periods of time during the year, some of whom become symptomatic during allergen seasons. Studies of desloratadine of 4 weeks duration or less show that patients receiving desloratadine experience significant reductions in symptoms scores compared with those receiving placebo (27, 28). While these patient groups are likely to contain patients with intermittent disease, it is not currently possible, however, to extract a subgroup of patients from these studies that conforms precisely to the definition of intermittent rhinitis.

Persistent rhinitis. In a multicenter, double-blind, placebo-controlled study of desloratadine 5 mg QD in patients with seasonal allergic rhinitis (SAR) and concomitant mild asthma, patients demonstrated active rhinitis (nasal and non-nasal symptoms) of at least moderate severity at baseline (29, 30). During the study, patients in both the desloratadine and placebo groups continued to exhibit active disease during the first 4 days, the first 15 days and across days 1–29, although symptom severities were significantly lower in the desloratadine group compared with placebo. Therefore desloratadine was effective in patients with active allergic rhinitis symptoms for more than 4 days and for more than 4 weeks (32 days, including active rhinitis during 3 days before baseline), indicating that this SAR study population met the ARIA definition of persistent rhinitis.

Simons et al. reported the results of a multicenter, double-blind placebo-controlled study of desloratadine 5 mg QD in patients with perennial allergic rhinitis (PAR) (31). In this study patients had active rhinitis (moderate symptoms) during the 3 days before baseline, and on the baseline day. Desloratadine significantly decreased symptom scores compared with baseline, however, both patient groups continued to have active rhinitis symptoms during the first 3 days, across the first 8 days, and across the full 29-day duration of the study. Thus this population of patients with PAR had active symptoms for more than 4 days per week and for more than 4 weeks (32 days, including active rhinitis for 3 days immediately before baseline, and on the baseline day).

Specific studies of desloratadine under the precise ARIA definitions of intermittent and persistent rhinitis have still to be performed. However, the results of studies of more than 4 weeks duration (29 days plus baseline assessments) in both seasonal and perennial rhinitis suggest that desloratadine is effective in patients with symptoms that were equivalent to persistent rhinitis according to the ARIA classification.

Effective for all nasal symptoms including nasal congestion

Meltzer et al. (28) reported the results of two multicenter, double-blind, placebo-controlled studies of desloratadine 5 mg QD in patients with SAR; one study was performed in the spring, the other in the autumn. At baseline all patients had active rhinitis, with moderate nasal and total symptom scores and mild-to-moderate non-nasal symptom scores. At week 1 and week 2 of the study decreases in nasal and non-nasal symptom scores were seen with desloratadine, compared with placebo during the spring and autumn studies. Berger et al. (29) also demonstrated the efficacy of desloratadine 5 mg QD against nasal and non-nasal symptoms of SAR in a 29-day study. The changes from baseline in total nasal and total non-nasal symptom scores were significantly greater with desloratadine compared with placebo during week 1–2 and across the full duration of the study. Individual nasal symptom scores (rhinorrhea, nasal stuffiness, nasal itching, sneezing) were all significantly reduced by desloratadine. In patients with PAR treated with desloratadine 5 mg QD

or placebo for 29 days, total nasal symptoms were reduced to a significantly greater extent from baseline than with placebo over the duration of the study (31). Similarly, the mean percentage reduction from baseline in reflective total non-nasal symptoms were decreased to a significantly greater extent with desloratadine compared with placebo across days 1–29.

Nasal obstruction is one of the most difficult to treat symptoms of allergic rhinitis, and the efficacy of antihistamines against this symptom has been queried. Desloratadine has demonstrated a beneficial impact on nasal congestion from a series of clinical studies in patients with allergic rhinitis. Nayak and Schenkel reported that in SAR patients treated with desloratadine 5 mg or placebo QD for 2 weeks, the decrease from baseline in nasal obstruction symptom scores was significantly greater with desloratadine on days 2, 3, and 4 and across the whole duration of the study (32). Other clinical studies of 2- and 4-week duration have also demonstrated significantly larger decreases in nasal obstruction with desloratadine compared with placebo (27, 29). Schenkel et al. compared the effects of desloratadine 5 mg QD, oral pseudoephedrine 240 mg QD or the combination of both drugs in the treatment of nasal obstruction for 14 days in patients with SAR (33). The magnitudes of the effects of desloratadine and pseudoephedrine monotherapies were not statistically different from one another, while the combination treatment had an additive effect on nasal obstruction.

Studies have indicated that the improvement in symptomatic nasal obstruction seen with desloratadine can be accompanied by improved objective measures of nasal airflow. Horak et al. studied the impact of desloratadine 5 mg or placebo QD for 7 days on nasal airflow and rhinitis symptoms, in two identical studies of grass pollen allergic patients (34, 35). Nasal airflow was measured repeatedly using active anterior rhinomanometry during a 6-h exposure to allergen in a highly controlled exposure unit. Patients treated with desloratadine had a significantly smaller allergen induced decrease from baseline in nasal airflow compared with placebo within 30 min of exposure, which lasted for 6 h. Nasal congestion symptoms were also significantly less after 15–30 min of exposure in the desloratadine group. Allergen exposure studies such as these add objective support to but do not supplant data from placebo-controlled clinical trials. Comparative trials of the effects of desloratadine and a topical nasal corticosteroid on nasal obstruction have not been performed; therefore, the relative magnitude of the impact of desloratadine on nasal obstruction remains to be ascertained.

Improvement of eye symptoms

In a 4-week study of desloratadine 5 mg or placebo QD, ocular symptoms such as itching/burning eyes, tearing/watering eyes and redness of eyes were significantly lower with desloratadine compared with placebo (29) (Fig. 4).

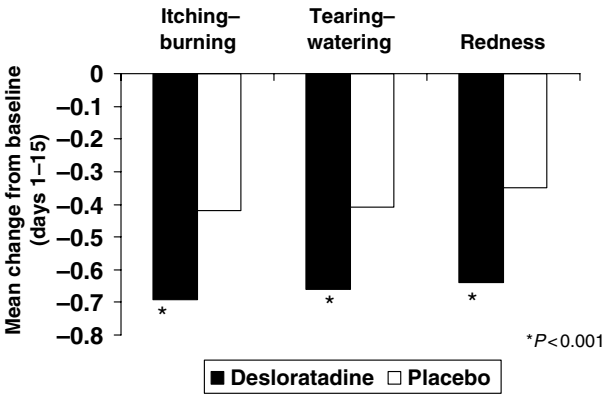

Figure 4. Mean decreases from baseline in ocular symptoms from days 1–15 with desloratadine 5 mg or placebo once daily in patients with seasonal allergic rhinitis and concomitant mild asthma. Adapted from Berger et al. (29) with the permission of Annals of Allergy, Asthma and Immunology.

Chest symptoms associated with allergic rhinitis. Patients with allergic rhinitis commonly suffer from asthma and vice versa (1). Studies in asthma commonly require an objective airflow measure, such as, an improvement in forced expiratory volume in 1 s (FEV_1) to demonstrate therapeutic efficacy. Patients with allergic rhinitis can suffer from bothersome concomitant seasonal chest symptoms (e.g. wheezing, cough, dyspnea), without a major decrement in airflow (1). These chest symptoms can be considered as important non-nasal symptoms of allergic rhinitis.

In a double-blind, placebo-controlled trial, 924 patients with SAR and concomitant seasonal chest symptoms received either desloratadine 5 mg, montelukast 10 mg or placebo QD for 4 weeks (30). Both desloratadine and montelukast treatment groups experienced a significant reduction from baseline in total and individual chest symptom scores compared with placebo over the duration of the study (Fig. 5). Desloratadine and montelukast also reduced inhaled β_2 agonist requirements compared with placebo. No significant differences were seen between desloratadine and montelukast during the study.

In accordance with the current labeling indications, no claims for efficacy in asthma or for preventative effects of desloratadine were made.

Studies should be carried out in children and elderly patients to assess efficacy

Desloratadine is approved for use in children aged 2–12 years, based on efficacy equivalence and safety data (3), but no specific efficacy study has yet been published. Specific efficacy studies have not been performed to date with desloratadine in the elderly.

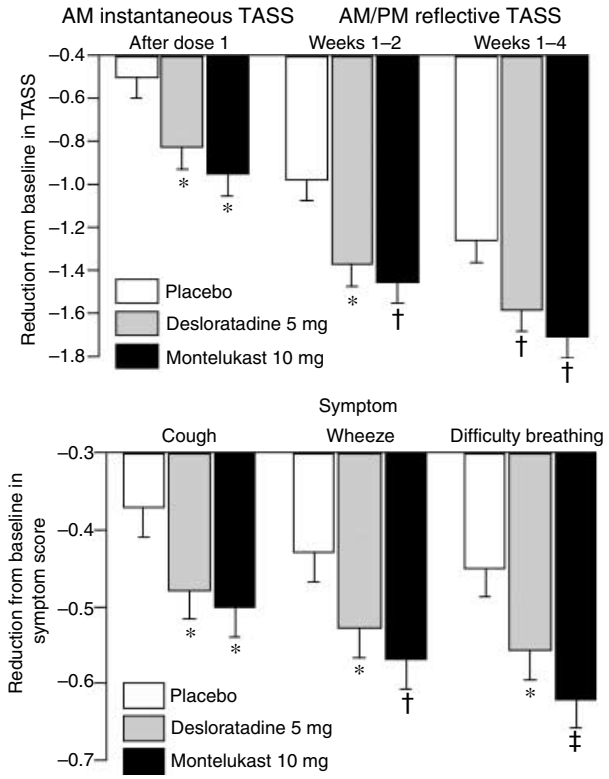

Figure 5. Effects of desloratadine 5 mg, montelukast 10 mg or placebo once daily for 4 weeks on total asthma symptoms score (TASS) rated AM and PM (upper figure), and on individual asthma symptoms scores (lower figure). $*P < 0.05$; $\dagger P < 0.01$; $\neq P < 0.001$ *vs* placebo. No significant difference between desloratadine and montelukast. Reproduced from Baena-Cagnani et al. (30), *International Archives of Allergy and Immunology*, 2003, with the permission of S. Karger AG, Basel.

Efficacy

- Desloratadine is effective in the treatment of seasonal and perennial allergic rhinitis
- Although no specific study has been done, by extension, desloratadine may be considered to be effective in persistent rhinitis as defined in the ARIA document, and is effective for all nasal symptoms including nasal congestion.
- Eye symptoms are also improved with desloratadine,
- Desloratadine can improve chest symptoms in patients with allergic rhinitis and concomitant seasonal asthma.

Side effects

No sedation or cognitive or psychomotor impairment

The term 'sedation' is commonly used to describe the subjective effects of an antihistamine on self-rated measures of sleepiness or somnolence. For the purposes of this review sedation was assessed with respect to data derived from clinical trials of desloratadine and detailed safety analyses contained in regulatory labeling documents.

Sedation. In placebo-controlled clinical trials of desloratadine 5 mg QD in SAR and PAR of 2 and 4 weeks duration, there was no statistical difference in the rates of sedation between desloratadine and placebo (3). The pooled population from allergic rhinitis studies was 4797. The overall rate of treatment-related treatment emergent adverse events was 14% for desloratadine and 12% for placebo ($P = $ NS). The rate of somnolence was 2% in both the placebo and desloratadine groups.

Cognitive or psychomotor impairment. Studies of the psychomotor effects of antihistamines should employ relevant measures that are sensitive to the effects of antihistamines. Ideally, studies of second-generation antihistamines should employ both a placebo-control and a sedating first-generation compound as an active control.

In studies of desloratadine that involved both placebo and active controls, desloratadine did not cause psychomotor or cognitive impairment. Nicholson et al. (36) conducted a single dose double-blind, crossover study of desloratadine 5 mg *vs* placebo and promethazine 25 mg (active control) in healthy volunteers. They found that desloratadine did not impact psychomotor performance, daytime sleep latencies or subjective measures of sedation. Desloratadine had no effect on subjective sleepiness or fatigue and the objective measures of tracking, choice reaction time, digit symbol substitution and attention were unaffected. Desloratadine had no consistent effect on memory. In contrast, all of the above measures, including memory, were consistently impaired by promethazine throughout the study.

Wilken et al. (37) conducted a double-bind, randomized, placebo- and active-controlled study of the effects of desloratadine 5 mg on neuropsychological performance in subjects with SAR. The study was performed out of the allergy season in an allergen exposure unit, in which subjects received fixed environmental levels of the relevant allergen. At 90 min postdosing, both desloratadine and the active control (diphenhydramine 50 mg) significantly reduced the symptoms of SAR compared with placebo. However, the diphenhydramine group had significant and clinically relevant performance decrements in terms of vigilance measures, cognitive measures and sleepiness scores compared with desloratadine. Desloratadine itself was not significantly different from placebo in any neuropsychological measure. Thus, desloratadine improved allergy symptoms without the cost of central nervous system impairment that was associated with a first generation antihistamine.

A further study of the effects of desloratadine 7.5 mg, diphenhydramine 50 mg and placebo on car driving (nonsimulated) showed desloratadine and placebo to be similar; diphenhydramine was associated with significantly

greater lateral weaving and a longer breaking reaction time *vs* placebo (3).

In a novel study design, Satish et al. (38) assessed the effects of desloratadine on simulated real-world performance in patients with SAR. Patients with symptomatic SAR were treated with desloratadine 5 mg QD, while asymptomatic patients received placebo. Patients then undertook a series of tasks appropriate to real-world work environments (managerial tasks, analysis, decision making). In patients with symptomatic SAR, treatment with desloratadine restored task performance to the control (asymptomatic) level or improved performance significantly. This study indicates that SAR has deleterious effects on performance that can be partially restored to normal levels by desloratadine treatment.

Desloratadine does not augment the psychomotor impairing effects of alcohol. In a single-dose, double-blind, randomized, placebo-controlled, crossover study, the relative effects of desloratadine 7.5 mg and placebo with or without alcohol were compared (3). There was no difference between the effects of desloratadine and placebo groups when assessed alone or with alcohol in terms of tests of cognition, vigilance and self-rated somnolence.

No anticholinergic effects

Desloratadine is a selective H_1 receptor antagonist that has no relevant effects on muscarinic receptors from *in vitro* and animal *in vivo* studies (4, 5). Results of clinical studies of desloratadine are in concordance with the lack of relevant affinity of desloratadine for muscarinic receptors. In a pooled analysis of four multiple-dose studies of desloratadine ($n = 659$) and placebo ($n = 661$) in SAR, the incidence of dry mouth was 3% in the desloratadine group and 2% with placebo (3). No other anticholinergic-related adverse events were reported by ≥2% of the study population. In a wider analysis that pooled 4797 subjects with allergic rhinitis treated with desloratadine or placebo, treatment related, treatment-emergent dry mouth occurred in 2–3% of both treatment groups (3). Similarly, chronic urticaria trials report a similar low incidence of dry mouth with desloratadine (2.8%) and placebo (2.9%) (3).

No weight gain

Weight gain has not been reported as a significant side effect of desloratadine therapy in individual and pooled analysis of clinical trials (3).

No cardiac side effects

The cardiac safety of desloratadine has been studied extensively in the preclinical and clinical settings. Inhibition at the level of the cardiac potassium channel encoded by the *human ether-a-gogo-related gene* (HERG) is associated with long corrected QT (QTc) on the electrocardiogram (ECG) (39). Desloratadine had no effect on HERG channels at clinically relevant and at high concentrations *in vitro* (40). After dosing with desloratadine at levels of 4 and 12 mg/kg in rats, no relevant changes were seen on the ECG including no effects on the QTc interval. Similarly, after high-dose intravenous administration of desloratadine in guinea pigs (12 mg/kg), no effect on the QTc was seen.

In healthy volunteers, desloratadine has been shown to have no clinically relevant cardiovascular effects, even with multiple dosing at nine times the clinical dose (3). In a double-blind, placebo-controlled comparison of desloratadine 45 mg QD and placebo for 10 days, no statistically significant change in QTc interval was seen in the desloratadine group.

Combination of the antihistamines terfenadine and astemizole with inhibitors of CYP3A4, such as erythromycin and ketoconazole, has been reported to lead to QTc prolongation and life-threatening ventricular tachyarrhythmias (39). When desloratadine 7.5 mg QD was administered to healthy volunteers in combination with ketoconazole 200 mg BID or placebo for 10 days, the combination of desloratadine and ketoconazole did not cause any clinically relevant changes in the QTc interval or other ECG measures (19). Also, when desloratadine was administered in combination with erythromycin in a similarly designed study, no impact on ECG parameters, including QTc, was noted (17).

The extensive database of information on the use of desloratadine in the clinical setting demonstrates that in 2469 SAR patients with evaluable ECGs before and during treatment, no patient experienced a treatment-emergent clinically significant ECG abnormality (3). One patient had a 7% increase in the QTc from 431 to 465 ms during desloratadine treatment, which was not associated with clinical symptoms or cardiovascular side effects. Overall, the mean QTc *decreased* by 1–4% in the desloratadine group, and decreased by 1% in placebo-treated patients. In a further pooled analysis in 966 patients who received desloratadine and 991 who received placebo, there was no appreciable effect of desloratadine on the QTc interval (3). Finally when groups of patients with normal ($n = 2393$), borderline ($n = 87$) or prolonged ($n = 19$) QTc intervals at baseline were considered separately, no evidence was found of an association of desloratadine with QTc prolongation (3).

Possible use in pregnancy and breast feeding

Desloratadine is not currently recommended for use in pregnant or breast-feeding women. Teratogenicity and mutagenicity studies in animals have shown no effect of desloratadine. Studies of the parent molecule, loratadine, in female patients during the first trimester of pregnancy have shown no adverse outcomes compared with matched cohorts (41, 42). As much of the ingested dose of loratadine is converted to desloratadine, these results indicate that desloratadine exposure during the first

trimester was also not associated with adverse pregnancy outcomes. As desloratadine is excreted into breast milk, it is not recommended for use by nursing mothers.

Studies should be carried out in young children and elderly age patients to assess safety

The safety of a syrup formulation of desloratadine has been studied in placebo-controlled studies in a pediatric population (3). The administered dose of desloratadine was 1.25 mg QD in children aged 2–5 years and 2.5 mg QD in children aged 6–11 years. Pooling the treatment groups gave a desloratadine population of 115 patients and a placebo group of 116 patients. The adverse event rates in the desloratadine and placebo groups were 7.0 and 10.3%, respectively. The most common adverse events were headache (1.7% desloratadine, 6% placebo), and fever (2.6% in each group). There were only two treatment-related adverse events with desloratadine [rash ($n = 1$), headache ($n = 1$)], both of which were mild in nature. No clinically significant cardiovascular or ECG changes were seen in the pediatric population (3).

Specific safety studies have not been performed in elderly populations. However, in a 10-day multiple dose study of desloratadine 5 mg QD, pharmacokinetic and safety data were collected prospectively in an elderly (65–70 years) subgroup (25). Elderly volunteers had a slightly elevated AUC for desloratadine (20% higher), but despite this increased exposure to desloratadine no increased rate of adverse events (including ECG measures) was seen.

Prospective postmarketing safety analyses should be conducted

A large, prospective, postmarketing study of desloratadine was reported by Bachert et al. (43), involving nearly 48 000 patients with SAR. The study, conducted in Germany under the stipulations of the Federal Institute for Drugs and Medical Products, collected information from patients and their physicians using a standardized questionnaire. The population consisted of 20 030 males (42.2%) and 27 452 females (57.8%). The mean duration of exposure to desloratadine was 38.4 days. Patients and doctors rated the tolerability to treatment separately on a 4-point scale at the end of treatment. Patients rated the tolerability of desloratadine as excellent, good, moderate and poor in 76.4, 22.1, 0.9, and 0.6%. The physician-rated tolerability was 79.2% (excellent), 19.7% (good), 0.6% (moderate), and 0.4% (poor). The overall adverse event rate was 0.44%, and no single treatment-related adverse event occurred at a frequency $>0.1\%$. The majority of adverse events were mild to moderate in severity. One patient with pre-existing metabolic liver disease developed gastrointestinal symptoms and tachycardia which were rated as severe by the study investigator and resolved with supportive treatment. The results of this practice-based study confirm the good tolerability profile of desloratadine reported in placebo-controlled clinical trials.

Side effects

- Desloratadine 5 mg daily is free from sedation and cognitive or psychomotor impairment.
- Desloratadine exhibits no anticholinergic effects.
- Weight gain has not been reported to occur during desloratadine treatment.
- Laboratory and clinical studies have shown desloratadine to be free from cardiac side effects.
- Safety studies have been performed in young children and elderly age patients,
- The safety profile of desloratadine derived from placebo-controlled clinical studies is confirmed by prospective postmarketing safety analyses.

Pharmacodynamics

Rapid onset of action

Onset of action in terms of control of allergic rhinitis signs and symptoms should be measured in an appropriate model (e.g. allergen exposure chamber) both following single dose administration and at steady state. Pharmacokinetic data indicate that desloratadine 5 mg is rapidly absorbed following oral dosing and reaches its C_{max} after 2.18 h (44). In a grass pollen allergen exposure study, single dose desloratadine 5 mg QD was associated with reduced SAR symptoms in 50% of individuals after 90 min and in all subjects within 3 h (45). In response to grass pollen allergen exposure at steady-state desloratadine conditions (5 mg daily for 7 days), the appearance of differences from placebo in terms of nasal symptoms and nasal airflow remained rapid, occurring 15–30 min after the beginning of exposure (34, 35).

Long duration of action, at least persistence of clinical effects at the end of the 24-h dosing period, so the drug can be administered once a day

In clinical studies of desloratadine 5 mg QD for the treatment of SAR and PAR, efficacy was seen following the first dose. In a randomized, placebo-controlled study of desloratadine 5 mg QD for 14 days in SAR, Meltzer et al. (28) reported a significant decrease in total nasal and total non-nasal symptoms at day 2. Similarly, Berger et al. (29) reported that the mean AM-rated total symptom score was significantly lower with desloratadine compared with placebo on day 2, (24-h postdosing) in patients with SAR. A further study of nasal congestion severity in patients with SAR demonstrated that this symptom was also significantly controlled on day 2, 24 h after the first dose (32). In patients with PAR, treatment with desloratadine 5 mg QD was also associated with a significantly lower total

symptom score on day 2 compared with placebo (31). The pharmacokinetic half-life of desloratadine 5 mg is 21–27 h, which supports the once daily dosing strategy for desloratadine (25, 44).

No likelihood of development of tolerance (tachyphylaxis)

Studies in allergic rhinitis with desloratadine have been performed for periods of approximately 2 or 4 weeks. Efficacy has been demonstrated for desloratadine compared with placebo in studies of SAR and PAR at the end of 29 days' treatment (29, 31), indicating that tolerance does not develop over normal study durations. Longer studies of desloratadine have yet to be performed in allergic rhinitis, although it is useful to note that tachyphylaxis was not seen in longer, 6-week placebo-controlled clinical trials of desloratadine 5 mg QD in chronic urticaria (46, 47).

Pharmacodynamics

- Desloratadine has a rapid onset of action, and a long duration of clinical efficacy.
- The clinical effect of desloratadine persists to the end of the 24-h dosing period.
- No tolerance/tachyphylaxis has been demonstrated with desloratadine.

Discussion

This review of the profile of desloratadine under the requirements of the ARIA/EAACI guidelines shows that desloratadine fulfils the majority of the criteria outlined at the outset in Table 1.

Pharmacokinetics

Desloratadine binds potently and selectively to the human H_1 receptor. The affinity of desloratadine for human muscarinic receptors is low and is unlikely to be relevant in the clinical setting. Clinically relevant concentrations of desloratadine have a significant inhibitory effect on the release of allergic inflammatory mediators by human leukocytes *in vitro*. Further studies would be useful to confirm these effects at the clinical dose in patients with allergic rhinitis. No clinically relevant interactions exist when desloratadine is co-administered with foods and common medications (including those metabolized by CYP3A4), and intestinal transport proteins have no impact on the pharmacokinetics of desloratadine. Desloratadine is not contraindicated in any specific disease group and caution is only recommended in patients with severe renal impairment.

Efficacy

Desloratadine is effective in the treatment of SAR and PAR. Further analysis of SAR and PAR studies of >4 weeks duration demonstrate that desloratadine exhibits clinical efficacy in patients who meet the criteria for a diagnosis of persistent allergic rhinitis. The efficacy of desloratadine has been demonstrated against all nasal symptoms, including nasal obstruction. The efficacy of desloratadine in nasal obstruction is supported by information from allergen exposure unit studies showing a reproducible impact on nasal airflow and nasal obstruction symptom scores in patients exposed to grass pollen allergen. Desloratadine is also effective against non-nasal symptoms of allergic rhinitis, including ocular symptoms and chest symptoms. Efficacy data in the elderly and pediatric populations would be useful to complete the efficacy profile of desloratadine in allergic rhinitis.

Side effects

Desloratadine is ostensibly free from sedation and somnolence in clinical studies, which is supported by a lack of objective impairment in specific neurocognitive studies that are sensitive to the impairing effects of sedating antihistamines. Desloratadine does not augment the sedating effects of alcohol. Desloratadine is free from anti-cholinergic effects in clinical trials, probably because of its selectivity for the H_1 receptor over other receptor subtypes. Weight gain has not been reported to be associated with desloratadine therapy. Extensive pharmacological studies (both *in vitro* and *in vivo*) and clinical data confirm that desloratadine is not associated with QTc interval prolongation or cardiovascular adverse events. The adverse event and tolerability profiles of desloratadine have been confirmed in a large postmarketing safety study involving approximately 48 000 patients. Desloratadine is currently not indicated for use by pregnant or nursing women.

Pharmacodynamics

In allergen exposure studies, the onset of action of desloratadine is 90 min after a single dose, while differences from placebo in terms of nasal symptoms and nasal airflow are seen within 15–30 min of allergen exposure at steady state conditions of desloratadine. In clinical studies, the efficacy of desloratadine was maintained through the 24-h dosing interval. No evidence of tachyphylaxis has been seen with desloratadine in 4-week studies in allergic rhinitis or in 6-week studies in chronic urticaria.

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