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Robert Seidman
Chief Pharmacy Officer
Pharmacy Department

April 15, 2002

Food and Drug Administration
Center for Drug Evaluation and Research (HFA-305)
ATTN: Jenny Butler
5630 Fishers Lane
Rockville, MD 20857

Dear Ms. Butler:

The undersigned submits this petition under the Code of Federal Regulations, Food and Drug Administration, Title-21, section 10.30. This regulation provides that drugs limited to prescription use under an NDA can be exempted from that limitation if the Food and Drug Administration ("FDA") determines the prescription requirements to be unnecessary for the protection of public health. By receipt of this letter, I am petitioning the FDA to make the following exemption:

On October 26, 1999, Schering-Plough Corporation filed its U.S. application for desloratadine for the treatment of seasonal allergic rhinitis (SAR). Desloratadine, according to the submission, is a non-sedating, long-acting antihistamine. Desloratadine is a metabolite of loratadine/Claritin®, also a Schering-Plough Corporation pharmaceutical. Desloratadine, according to Schering-Plough Corporation's submission to the FDA, has a safety profile identical to loratadine/Claritin® and is featured in direct to consumer (DTC) advertising as having side effects similar to a sugar pill. The clinical trials to date (including ones evaluating SAR, SAR with concomitant asthma, perennial allergic rhinitis, and chronic idiopathic urticaria) have reported similar incidences of adverse effects between desloratadine and placebo. Loratadine/Claritin® has been previously discussed with the FDA under Title-21, section 10.30 in the Petition docket number 98P-0610/CP1 and has been deemed approvable by the FDA to convert to over-the-counter (OTC) status.

Patients are seeking greater ownership of their health care and often prefer to self medicate when feasible. Of all the therapeutic classes of drugs available, the discrepancy in safety between the antihistamine and antihistamine/decongestant combinations currently available OTC compared to desloratadine is most pronounced. Based on the information provided by Schering-Plough Corporation in their submission for desloratadine and supplemental information provided in this petition, please expedite an OTC approval for desloratadine.

Currently, the FDA has authorized over 100 different antihistamine and antihistamine/decongestant combinations for OTC sale. Although considered safe and effective by the FDA, all OTC antihistamine and combination antihistamine/decongestant combinations are non-selective and have a more significant sedative and anticholinergic effect than the three leading prescription antihistamine and antihistamine/decongestant products. The safest antihistamine and antihistamine/decongestant combination medications are available only by a prescription. Based on this information, desloratadine, the metabolite of loratadine/Claritin®, should also be allowed to be available OTC.

The FDA approved loratadine/Claritin® DTC advertising makes claims that the incidence of side effects with loratadine/Claritin® is no different than that obtained when ingesting a sugar pill. Since Schering-Plough Corporation's NDA for desloratadine includes data illustrating a similar safety and efficacy profile for that of loratadine/Claritin®, it should be appropriate for desloratadine to be available OTC. Desloratadine (Aerius in Canada) can already be purchased without a prescription in the Canadian provinces of Quebec and British Columbia. It is our belief that Aerius (desloratadine) will be available OTC in all

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Canadian provinces in the near future. Attached, please also find a review of the medical literature supporting the OTC status of desloratadine.

The undersigned certifies that, to the best knowledge and belief of the undersigned, this amended Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Respectfully,



Robert C. Seidman, Pharm.D., M.P.H.
Chief Pharmacy Officer
WellPoint Health Networks

cc: Sandra Titus, FDA
Douglas Schur, WellPoint Health Networks



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Robert Seldman
Chief Pharmacy Officer
Pharmacy Department

April 17, 2002

Food and Drug Administration
ATTN: Jenny Butler
5630 Fishers Lane (HFA-305)
Rockville, MD 20857

Dear Ms. Butler:

Pursuant to Section 10.30, Section C of the Food and Drug Administration, we are requesting an exception to provide an environmental assessment under Section 25.24 for the conversion of Clarinex (desloratadine) from prescription to over-the-counter (OTC) status. Since Clarinex is a metabolite of a drug (Claritin/loratadine) that is already widely used, the conversion from prescription to OTC status will not result in the introduction of any additional drug substances into the environment. We appreciate your waiving of the environmental assessment provision for this important petition.

Respectfully,





Non Sedating Antihistamines Literature Review

I. INTRODUCTION

The prevalence of allergic rhinitis has been increasing in the past two to three decades.⁷² Approximately 9.3% to 30% of adults and up to 40% of children in the US have allergic rhinitis.^{1,73,74,75} Allergic rhinitis is not a condition associated with mortality; however it may impact an individual's quality of life, causing sleep and concentration disturbances, loss of taste, and general discomfort. Allergic rhinitis has a significant cost impact, with an estimated \$1-\$3.5 billion spent annually on the direct cost of disease and an additional \$3.8-\$5.2 billion in lost productivity both at home and at work.^{73,76,77,78} Self management of allergic rhinitis through the use of OTC antihistamines has already been approved by the FDA for a multitude of first generation antihistamines and most recently for loratadine, a second generation antihistamine. The purpose of this review is to provide clinical and safety data in support of the OTC status for desloratadine through an amendment to petition docket 98P-0610/CP1.

Allergic rhinitis may be seasonal, caused by pollens, pollen fragments, or mold spores, or perennial, due to allergens such as dust mites, mold, cockroaches, and animal dander.² For both seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), treatment is focused on alleviating the nasal and ocular symptoms, including itching, tearing eyes, rhinorrhea, nasal itching and congestion, sneezing, cough, headache, and throat irritation. Nonpharmacologic treatments—eliminating or reducing allergen exposure, use of air conditioners and dehumidifiers, and saline nasal sprays—may be of some benefit. However, for many patients, drug therapy is needed. Agents used in the treatment of allergic rhinitis include topical and oral decongestants, intranasal corticosteroids, mast cell stabilizing agents, topical antihistamines, and oral antihistamines. It should be mentioned that a number of recent analyses have shown the nasal steroids to be superior to second generation antihistamines in the treatment of allergic rhinitis and to be more cost effective.

Currently, there are four second generation antihistamines available in the US: loratadine, fexofenadine, cetirizine, and desloratadine.

II. PHARMACOLOGY

All of the antihistamines exert their pharmacologic effects by competitively and reversibly blocking the actions of histamine at the H₁ receptor.³ These agents do not inhibit the release of histamine from mast cells, nor do they bind to histamine itself. H₁ receptors are found both centrally and peripherally. First generation antihistamines (such as diphenhydramine, chlorpheniramine, and hydroxyzine) are nonselective H₁ antagonists, binding to central and peripheral H₁ receptors. This nonselectivity results in a higher incidence of centrally-related adverse effects, including CNS depression or stimulation. The first generation H₁ receptor antagonists also have stronger anticholinergic properties, exhibiting antiemetic effects. In contrast, the second generation antihistamines (loratadine, desloratadine, fexofenadine, and cetirizine) are selective for peripheral H₁ receptors, producing less centrally mediated effects, such as sedation, with few anticholinergic effects. Of the second generation antihistamines available, cetirizine is a piperazine derivative and is the active metabolite of hydroxyzine, whereas fexofenadine, loratadine, and desloratadine are all piperidines.^{1,3,4}

Table 1. Pharmacologic Effects of Second Generation Antihistamines³

Agent	Relative pharmacologic effects			
	Sedative	Antihistaminic	Anticholinergic	Antiemetic
Loratadine	low to none	moderate to high	low to none	N/A
Desloratadine	low to none	moderate to high	low ¹	N/A
Fexofenadine	low to none	moderate to high	low to none	N/A
Cetirizine	low to none	moderate to high	low to none	N/A
Diphenhydramine ²	high	low to moderate	high	moderate to high

N/A = not available; ¹Anticholinergic effects have been seen in some in vitro studies⁴⁰; ²Included for comparison of pharmacologic effects

In addition to their effect on histamine, a number of second generation agents appear to possess anti-allergy effects that cannot be explained by blocking histamine receptors alone. The potential of these agents to inhibit influx or activation of pro-inflammatory cells has been an area of intense research.³⁶ A large number of in vitro trials have been performed assessing the effect of various agents on mediator release from inflammatory cells. While many of these studies use concentrations of drug that are hundreds to thousands of times higher than those achievable in vivo, those using clinically achievable concentrations found that available second generation antihistamines all possess some degree of inhibitory effect on mediator release from cells.^{6,36,38} In vivo studies have shown a multitude of anti-inflammatory effects with these agents, perhaps most significantly with cetirizine and desloratadine.^{36,54} However, the clinical relevance of these findings as well as the practical differences between agents is not clear at this time.

The relative potency of the second generation antihistamines is generally determined by their ability to block intradermal histamine-induced wheal and flare reactions in the skin, although this is not necessarily predictive of clinical efficacy. A recent double-blind, cross-over trial compared cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine with placebo on this measure. The rank order of inhibitory effect was cetirizine, epinastine, terfenadine, ebastine, fexofenadine, loratadine, and placebo.³⁹ Comparative intradermal studies with desloratadine are not available. Based on the in vitro evaluation of IC-50, desloratadine appears to be 14-fold more potent than loratadine at blocking the H₁ receptor.⁵⁴ An in vitro study in the Chinese hamster ovary model characterized desloratadine as having a relative potency of 201 compared to 3.7, 1.2, and 1.0 for cetirizine, loratadine, and fexofenadine, respectively.⁷⁰

Although the intradermal histamine-induced wheal and flare model is often used to address onset of action in addition to potency, the onset of action of antihistamines in SAR does not always correlate with this measure. Better measures of in vivo onset of action may be obtained using other methods such as nasal challenge in environmental exposure units.⁵ In one unpublished, controlled pollen challenge study of 28 patients with SAR, desloratadine 5mg was found to have an onset of action of about 28 minutes.⁴¹ The onset of effect was defined as the time to a 28% drop in nasal and non-nasal symptom scores. However, based on a pooled analysis of four placebo-controlled seasonal allergic rhinitis trials, a 5mg dose of desloratadine offered an onset of action between 75 minutes and 2 hours.⁶⁹ When fexofenadine 60mg, 120mg, or 180mg was compared with loratadine 10mg using the intradermal histamine-induced wheal and flare model, the onset of action of fexofenadine was ≤ 2 hours and was significantly faster than loratadine ($p < 0.05$).⁷⁰ Another study using the same model showed significant inhibitory effects for loratadine were delayed up to 4 hours compared to cetirizine, terfenadine, astemizole, and chlorpheniramine.⁵ When evaluating the onset of effect in seasonal allergic rhinitis, clinical trials have shown loratadine to have significant efficacy starting 30 minutes after ingestion. An environmental challenge unit study of terfenadine, astemizole, cetirizine, and loratadine revealed cetirizine to have the quickest onset of definitive relief (2 hours 6 minutes)

followed by terfenadine (2 hours 17 minutes), loratadine (2 hours 37 minutes), and astemizole (2 hours 55 minutes) using survival analysis ($p=0.01$).⁷⁹ As can be seen, the variety of study designs and outcome measures used in these trials makes inter-study comparisons difficult.

III. PHARMACOKINETICS

The basic pharmacokinetic properties of the second generation antihistamines are given in Table 2. Following oral administration, loratadine is rapidly absorbed and undergoes extensive first-pass metabolism to an active metabolite (desloratadine) which represents 1% to 2% of the dose.⁵ The parent compound and its metabolite are then metabolized by cytochrome P4503A4 and possibly the P4502D6 isoenzymes and are subsequently excreted in the urine (42%) and feces (40%). Food has no significant effect on the bioavailability of loratadine.³ Desloratadine is the active major metabolite of loratadine.⁶ Following absorption, desloratadine is metabolized to 3-hydroxydesloratadine by unidentified enzymes, followed by glucuronidation.^{4,7} Eighty-seven percent of a dose of desloratadine has been found in the urine and feces as metabolites. In 7% of individuals, the metabolism of desloratadine is slow and systemic exposure to the drug is higher than in those who are not slow metabolizers. The frequency of slow metabolism is higher in some ethnic groups (e.g. 20% in blacks).⁴ The bioavailability of desloratadine is unaffected by food.^{46,47} The absolute bioavailability of fexofenadine is unknown, however, the drug is rapidly absorbed.⁸ Only about 5% of a total dose is thought to be metabolized, with most of the drug excreted unchanged in the urine (80%) and feces (11%). Administration with food does not have a clinically significant effect on the rate or extent of absorption of fexofenadine.⁷⁰ For cetirizine, most of the drug is eliminated unchanged in the urine (70%), with only a small amount found as metabolites.⁹ Although hepatic metabolism is not a major route of elimination for cetirizine, studies suggest that a lower dose may be required in patients with hepatic dysfunction, as well as for patients with renal impairment. Food also has no effect on the bioavailability of cetirizine.⁷¹

Table 2. Pharmacokinetics of Second Generation Antihistamines^{3,4}

Agent	Time to maximum concentration (T_{max})	Elimination half-life ($t_{1/2}$)	Usual dosing interval	% protein binding	CYP450 metabolism
Loratadine	1.3-2.5 h	8.4-28 h ¹	24 h	97% ²	Yes
Desloratadine	3 h	27 h	24 h	82%-89% ¹	No
Fexofenadine	2.6 h	14.4 h	12 h (24 h for the SR preparation)	60-70%	No
Cetirizine	1 h	8.3 h	24 h	93%	No

¹For parent compound and active metabolite. ²Not measured with plain tablets, only with D products.

IV. CLINICAL EFFICACY

Allergic Rhinitis

A number of comparative trials have been conducted between the older second generation antihistamines. Overall, similar efficacy has been seen between agents. In general, these agents are most effective in providing relief from rhinorrhea, sneezing, and itching. Their efficacy in relief of nasal congestion is more variable. Table 3 reviews selected comparative trials between agents.

Table 3. Clinical Trials of Second Generation Antihistamines for Allergic Rhinitis¹⁰⁻²²

Reference	# pts/duration	Regimen	Outcomes
Loratadine			
Al-Muhaimeed 1997	84 pts (1 wk)	Loratadine 10mg or astemizole 10mg daily	Mean nasal symptoms scores were ↓ in both groups and were similar between txs (except for runny nose scores, which favored astemizole [p=.008]). The % of pts rated as good or excellent by global assessment were ↑ with astemizole (87% vs 62%) as were the % of pts who were sx-free (54% vs 39%); however, statistical analyses were not given.
Chervinsky et al 1994	167 pts (8 wks)	Loratadine 10mg or astemizole 10mg daily	Both agents were effective in ↓ total, nasal, and nonnasal sxs scores from baseline w/no sig diff between the 2 tx groups. Loratadine was favored for improvements in ocular symptoms (tearing and redness, p<.04). MD and pt assessments indicated earlier response w/loratadine, with improvements noted at 1 week. The 2 txs were equivalent at later time points.
Day et al 1997	111 pts (Single dose following allergen challenge)	Loratadine 10mg, astemizole 10mg, cetirizine 10mg, terfenadine 60mg, or placebo	Onset to time of relief was fastest w/cetirizine; however, the differences were not sig between the active tx groups. The % of pts w/clinically important relief was similar between the tx groups. Cetirizine was ranked highest on global assessments for time to relief and relative efficacy.
Crawford et al 1998	14 pts (8 wks— 2 wk crossover trial)	Loratadine 10mg, terfenadine 120mg, astemizole 10mg, chlorpheniramine 16mg per day	Overall efficacy scores, patient-reported symptoms, and pseudoephedrine use were similar between the tx groups. All 4 txs improved sxs from baseline as assessed by MD nasal-exam scores; however astemizole was rated sig ↑ than loratadine (p<.05).
Carlsen et al 1993	76 pts (4 wks)	Loratadine 10mg or terfenadine 120mg per day	Both txs associated with sig ↑ from baseline in sxs. 78% of loratadine- and 80% of terfenadine-treated pts were considered responders. All 7 pts who did not respond to terfenadine improved with loratadine, while only 4/9 pts who did not respond to loratadine responded to terfenadine.
Del Carpio et al 1989	317 pts (2 wks)	Loratadine 10mg, Terfenadine 120mg, or placebo per day	Both active txs were ↑ effective in improving nasal and non-nasal allergy sx severity scores. However, only loratadine reached sig in comparison to placebo at end of the study. 58% of loratadine-tx and 51% of terfenadine-tx pts had good or excellent response to tx as compared to 27% of the placebo group (p<.01).
Cetirizine			
Lockey et al 1996	311 pt (2 wks)	Cetirizine 10mg, terfenadine 120mg, or placebo daily	At 1 week, cetirizine resulted in sig ↑ in total sx scores as compared to terfenadine or placebo (p=.001); however no difference was seen between the 3 groups at 2 wks
Renton et al 1991	60 pts (6 wks; 3 wk crossover trial)	Cetirizine 10mg or terfenadine 120mg daily	Both txs were = effective in relieving sxs based on investigator scores; however cetirizine was more effective in relieving sxs of rhinorrhea. There was no difference in pt scored symptoms between the 2 treatments.
Lobaton et al 1990	30 pts (12 wks; 4 wk crossover trial)	Cetirizine 10mg or astemizole 10mg daily	Both cetirizine and astemizole were effective in improving nasal sxs with no sig differences btx the 2 groups based on investigators assessments. However, pt assessments rated improvements with cetirizine higher (p=.0001).
Meltzer et al 1996	279 pts (2 days)	Cetirizine 10mg, loratadine 10mg, or placebo	Cetirizine produced sig ↑ reductions in mean sx complex scores during 3 of the 4 time periods evaluated. However, changes with loratadine similar to those seen with placebo. Total sx complex severity scores were sig better with cetirizine at each time period tested. The onset of action found to be faster with cetirizine.
Fexofenadine			
Van Cauwenberge 2000	688 pts (2 wks)	Fexofenadine 120mg, loratadine 10mg, or placebo daily	509 pts were included in the ITT analysis. Fexofenadine and loratadine sig ↓ mean scores for reflective (previous 24h) and instantaneous (previous hour) total sx scores (TSS; sneezing, rhinorrhea, itchy nose, palate, and/or throat, itchy/watery/red eyes) from baseline. Fexofenadine was sig better for sxs of nasal congestion and itchy/watery/red eyes. However, overall tx efficacy was similar between the 3 grps, based on MD and pt assessments. Although all 3 groups had sig ↑ from baseline in quality of life scores, fexofenadine had greatest ↑ compared to loratadine and placebo.
Prenner 2000	659 pts (30 days; crossover after 14 days for nonresponders)	Fexofenadine 120mg or loratadine 10mg daily	At the end of 14 days, 389 pts were considered responders (61% of loratadine grp, 57% of fexofenadine grp). Pts given loratadine had a sig greater ↓ in TSS compared to fexofenadine (p=.019). No difference was seen btx the 2 groups based on investigator assessment of sx severity. Among nonresponders, 62.4% had complete, marked, or moderate relief of sxs when switched to loratadine, compared to 51.2% when switched to fexofenadine (p=.005). Failure rates ↑ after the switch to fexofenadine than to loratadine (21.7% vs 10.6%, p=.011).
Howarth 1999	842 pts (2 wks)	Fexofenadine 120mg, fexofenadine 180mg, cetirizine 10mg, or placebo daily	All txs resulted in a ↓ in reflective TSS from baseline, with no sig differences seen between the active tx groups. For individual symptom scores and for instantaneous TSS, all 3 active txs were sig more effective than placebo.

Published studies of the efficacy of desloratadine are limited and there are no published trials comparing it to other second generation agents. As part of the FDA approval process, the efficacy and safety of desloratadine for SAR was evaluated in 4 multiple-dose studies. The primary endpoint of the multiple-dose SAR studies was defined as the average prior 12-hour, “reflective” (i.e. symptom severity was assessed over the prior 12 hours) AM/PM total symptom score. The total symptom score was the sum of eight individual symptom scores---4 nasal (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and 4 non-nasal (itching/burning eyes, tearing/watering eyes, redness of eyes, itching of ears and palate). Results from the 4 multiple dose studies are provided below in Table 4. One study (C98-225) failed to demonstrate a difference between desloratadine and placebo.

Table 4. Total Symptom Score AM/PM Prior 12-Hour Average for Days 2-15

Treatment Group	Baseline		Change from Baseline			Placebo Comparison (p-value)
	(N)	(mean)	(N)	(mean)	(%)	
Study C98-001⁵³						
5.0 mg	172	14.2	172	-4.3	-28.0%	<0.01
Placebo	174	13.7	174	-2.5	-12.5%	---
Study C98-223⁵⁸						
5.0 mg	165	16.3	165	-4.6	-27.8%	0.03
Placebo	165	16.5	163	-3.5	-21.7%	---
Study C98-224⁵³						
5.0 mg	164	17.0	164	-5.1	-30.0%	0.02
Placebo	164	17.1	164	-3.8	-22.0%	---
Study C98-225⁵⁸						
5.0 mg	158	16.8	157	-4.2	-24.6%	0.41
Placebo	158	17.0	158	-3.8	-22.3%	---

Individual symptom scores including nasal congestion/stuffiness, nasal discharge/rhinorrhea, nasal itching, sneezing, itchy/burning eyes, tearing/watering eyes, redness of eyes, and itching of ears/palate were collected as secondary endpoints in the 4 multiple-dose studies. The results are presented in Table 5. Only one of the four studies (C98-001) demonstrated any difference from placebo in the “nasal congestion/stuffiness” symptom score.

Table 5. Individual Nasal and Non-Nasal Symptom Scores AM/PM Prior 12-Hours for Days 2-15.

Symptom	Study Number			
	C98-001 ⁵³	C98-223 ⁵⁸	C98-224 ⁵³	C98-225 ⁵⁸
Nasal congestion/stuffiness	-21.3%*	-20.1%	-23.3%	-18.2%
Nasal discharge/rhinorrhea	-22.0%**	-22.9%	-25.9%	-18.5%
Nasal itching	-29.5%**	-24.6%	-28.6%*	-22.6%
Sneezing	-32.1%**	-30.2%*	-34.9%**	-23.7%
Itching/burning eyes	-27.2%**	-29.5%*	-32.1%*	-27.8%
Redness of eyes	-23.9%**	-27.7%*	-29.8%*	-24.4%
Tearing/watering eyes	-25.4%**	-32.9%*	-29.6%	-30.6%
Itching of ears/palate	-25.9%**	-29.1%*	-33.5%*	-25.6%

*p≤ 0.05 **p≤ 0.01 **Bolded** figures represent NON-statistical significance from placebo

(Mean change from baseline for 5.0mg dose. P values reflect comparison to placebo treatment.)

As part of the desloratadine development program, a trial was conducted where the individual symptom of nasal congestion in patients with SAR was specified as the primary endpoint.⁵⁸ In this trial, desloratadine failed to differentiate from placebo in the reduction of nasal congestion.

An unpublished study of the 24-hour efficacy of desloratadine 5mg daily evaluated 282 patients with SAR over 4 weeks. Researchers found the 24-hour TSS decreased by 16.5% after the first dose versus 6.7% with placebo (p<0.05) and 28.1% from days 1 to 29 versus 20.9% with placebo (p<0.05).⁵⁵

Unlike the results presented earlier, a number of *unpublished* analyses of pooled data of patients with SAR have revealed that desloratadine results in significant nasal decongestion compared to placebo. The nasal decongestion efficacy was maintained over the duration of the trials.^{56,57} A multicenter, double-blind, placebo-controlled trial evaluated the ability of desloratadine to relieve symptoms of nasal congestion in 326 patients with SAR and mild-to-moderate asthma symptoms.⁶³ Patients were randomized to desloratadine 5mg daily or placebo for 4 weeks. Compared to placebo, desloratadine improved the average AM/PM reflective congestion score by 26.8% over baseline (p=0.014) at 4 weeks. Desloratadine 5mg daily was compared to placebo over 4 weeks in a randomized, double-blind trial of 331 patients with SAR and asthma.⁶⁵ Significant reductions in nasal congestion were noted with desloratadine after the first dose (-18.3% vs -10.1% with placebo; p<0.011). Overall total symptom scores were significantly reduced with desloratadine compared to placebo (p=0.001).

In one double-blind trial, 346 patients were randomly assigned to treatment with either desloratadine 5mg or placebo once daily for 2 weeks. Patients rated symptoms of nasal congestion or stuffiness twice daily, on a scale of 0 (none) to 3 (severe). Other symptoms of intermittent allergic rhinitis—including rhinorrhea, nasal itching, sneezing, itching/burning or tearing/watering eyes, eye redness, and ear or palate itching—were also assessed by the patients.²³ Reductions in morning and evening nasal congestion scores were significantly lower with desloratadine compared to placebo (p<0.05), beginning on day 2 of treatment. Total symptom scores also decreased from baseline with desloratadine, with a significantly greater reduction than seen with placebo (p<0.01).

An unpublished retrospective literature evaluation of double-blind, placebo-controlled trials of cetirizine, fexofenadine, and loratadine compared the reported effects of these agents on nasal congestion to that of desloratadine 5mg daily.⁶⁴ Only trials that specifically reported the effects on nasal congestion and used clinically approved drug doses were included. Placebo effects of the agents were factored out and standardization of severity scores was performed. The pooling and standardization of the desloratadine data resulted in a reduction in congestion of 0.1-0.19 units from baseline. In trials of fexofenadine (60mg BID - 120mg QD), congestion was reduced by 0.064-0.088 units. Cetirizine (10mg QD) and loratadine (10mg QD) reduced congestion by 0.08 and 0.03-0.1 units, respectively. Statistical analyses of these reductions were not reported.

Asthma

The role of histamine in asthma is well established. Histamine has the potential to cause smooth muscle contraction, mucus hypersecretion, mucosal edema, and bronchial hyperresponsiveness in sensitive individuals. The additional anti-inflammatory effects make them potential adjuncts to traditional asthma therapy.

Cetirizine 15mg daily for 14 days in 57 patients with pollen-associated asthma resulted in a decrease in pulmonary symptoms with a decrease in the use of beta-agonists and corticosteroids compared to placebo.⁸⁰ Another randomized, double-blind trial enrolling 43 subjects with grass pollen-induced asthma evaluated the effects of cetirizine 10mg BID and terfenadine 60mg BID. The results of the trial showed that cetirizine was significantly better than terfenadine at improving nasal obstruction, dyspnea, morning peak flow, consumption of beta-agonists, and the efficacy index on asthma (p<0.05).⁸¹ Other studies were unable to demonstrate a significant protective effect with cetirizine on allergen-induced bronchospasm.^{82,83} Cetirizine has also been shown to significantly improve asthma symptoms, although not peak flow or FEV₁, in patients with concomitant SAR and asthma in a number of studies.^{84,85,86} In a small number of patients, loratadine did not have a significant effect on symptoms or peak flow either alone or as adjunctive therapy.^{87,88} However, a larger more recent study using loratadine with pseudoephedrine found that the combination significantly improved pulmonary function as well as rhinitis and asthma symptoms.⁸⁹

A double-blind, placebo-controlled unpublished study of desloratadine in 278 patients with concurrent SAR and mild asthma symptoms evaluated patients over 2 weeks of treatment.⁶⁰ With desloratadine 5mg daily, the total asthma symptom score improved from baseline ($p<0.05$ vs placebo). In addition, the use of inhaled beta-agonists was decreased from baseline ($p=0.002$ vs placebo). Another unpublished placebo-controlled trial evaluated desloratadine 5mg daily in 604 patients with SAR and mild-to-moderate asthma over 4 weeks.⁶² Compared to placebo, desloratadine significantly reduced the total asthma symptom score (TASS) after the first dose ($p<0.05$). The reduction in TASS was maintained throughout the study ($p=0.022$). In addition, desloratadine significantly reduced the use of inhaled beta-agonists over the duration of the study ($p=0.003$).

Another area of research is the potential for these agents to prevent the progression to allergic asthma from atopic dermatitis. A double-blind, placebo-controlled trial evaluated cetirizine 0.5mg/kg/day over 18 months in 800 children at risk of developing allergic asthma. This study showed that in those sensitized to pollen or house dust mites, cetirizine halved the number of children developing asthma.⁹⁰

Chronic Idiopathic Urticaria

Although not the focus of this review, antihistamines are widely used in the treatment of chronic idiopathic urticaria (CIU). The primary target of therapy for urticaria is relief of pruritis, which is the most bothersome symptom for these patients. Although the first generation agents may offer the fastest onset of action and the greatest potency, their problematic side effects have resulted in a preference for the second generation products for this indication. It should be noted that often doses that are twice the usual recommended dose for these products are required for the treatment of CIU, which may result in some degree of sedation. Loratadine, fexofenadine, and cetirizine all possess FDA-approved indications for the treatment of urticaria. Desloratadine is not yet approved for this indication but a number of trials have been performed to investigate its efficacy.

A double-blind, placebo-controlled trial of 190 patients with CIU currently in flare compared desloratadine 5mg daily to placebo for 6 weeks.⁶¹ Significant improvement in the mean AM/PM reflective pruritis score was seen (-45.2 vs -14.0% ; $p<0.001$) within 36 hours of the first dose. The mean reflective total symptom score was also significantly reduced with desloratadine after the first dose (-41.6 vs -10.6 ; $p<0.001$). The reduction in the reflective pruritis score was maintained for the duration of the study ($p<0.001$ vs placebo) as was the total symptom score compared to placebo ($p<0.001$). During the final week of the trial, the improvement in sleep with desloratadine was 75% compared to 54% with placebo ($p\leq 0.03$). Similar improvements were seen in daily performance (78% with desloratadine vs 40% with placebo; $p<0.001$). A number of unpublished trials have also shown desloratadine to significantly decrease individual symptoms (pruritis, number of hives, size of largest hive), total symptoms scores, interference with sleep and daily activities.^{66,67,68}

Antihistamine/Decongestant Combinations

Three of the second generation antihistamines—loratadine, fexofenadine, and cetirizine—are available in combination with a decongestant, pseudoephedrine. Currently, no studies are available comparing these various antihistamine/decongestant combinations to each other. Table 6 provides a brief overview of trial assessing efficacy with combination therapy.

Table 6. Second Generation Antihistamine/Decongestant Combinations²⁴⁻²⁶

Reference	No pts/duration	Regimen	Outcomes
Sussman 1999	651 (14-20 days)	Fexofenadine 120mg, pseudoephedrine 250mg, or Fexofenadine/ pseudo-ephedrine 120/250 mg daily	The combo therapy was sig better than pseudoephedrine alone (p<.001) in ↓ the reflective TSS (minus nasal congestion scores); however, there was no sig difference btx combo and fexofenadine alone (p=.1579). For nasal congestion scores, the combo was better than fexofenadine alone (p<.005), but not better than pseudoephedrine alone (p=.059).
Kaiser 1998	469 pts (2 wks)	Loratadine/pseudo-ephedrine 5mg/120mg 2X daily, loratadine/ pseudoephedrine 10mg/240mg 1x daily, or placebo	Compared to placebo, both active txs resulted in sig ↓ from baseline in total nasal (TNSS) and non-nasal (TnNSS) symptom scores, and in TSS. Reductions in TNSS were similar between the 2 active txs, while the 10/240 mg combination was more effective in ↓ TnNSS and TSS compared to the 5/120mg combination. Mean ↓ in individual sx scores for rhinorrhea and nasal stuffiness were sig ↓ from baseline for the 2 active txs compared to placebo at study endpoint.
Horak 1998	24 pts (1 wk; crossover after 2 wks)	Cetirizine/pseudo-ephedrine 5mg/120mg or placebo 2x daily	Following allergenic challenge, a single dose of cetirizine/pseudoephedrine was sig ↑ than placebo in relieving sx (nasal obstruction, running/itching nose, sneezing), improving overall sx scores, and in overall subjective sx. Overall, objective parameters (nasal airflow, nasal secretions, nasal patency) also improved. After multiple dosing, similar results found w/active tx resulting in sig improvements in subjective and objective measures.

V. ADVERSE EFFECTS

Overall, the second generation antihistamines are well tolerated.^{1,3,27} Their primary advantage is their relative lack of sedation compared to first generation agents. However, it is useful to review the problems associated with the measurement of sedation.³⁶ Terms such as sedation, drowsiness, or sleepiness are often thought of interchangeably, but are actually quite different. Sedation means impairment of cognitive and psychomotor functioning and can be measured objectively. Drowsiness is the increased likelihood of falling asleep and is a subjective or objective measure depending on the means of measurement (subjective survey versus EEG). An interesting phenomenon is that patients may be unaware of changes in levels of cognitive and motor impairment. Therefore, significant disagreement may be seen in objective and subjective measures of impairment. To further complicate matters, it is known that allergic rhinitis itself leads to performance and learning impairment.³⁷ As a result, studies of sedation employing normal volunteers may not accurately represent actual use situations.

In addition to low sedation potential, these agents possess a relative lack of anticholinergic effects as compared to the first generation products. Although cetirizine is considered a second generation agent, it possesses a different sedation potential than other agents in the class. Cetirizine, the active metabolite of the first generation antihistamine hydroxyzine, has been described as a low-sedating, rather than non-sedating. The incidence of reported sedation or somnolence with cetirizine has varied, ranging from 13.7% to 25% and may be dose-related. Additionally, cetirizine has been reported to impair driving abilities in patients receiving the drug, while these effects were not reported with loratadine. Overall, both objective and subjective measures of sedation are conflicting for cetirizine and the lack of a standard approach to study designs makes meta-analysis difficult.³⁶ The sedative effects of cetirizine may be potentiated by alcohol, producing more sedation than either the drug or alcohol alone.^{1,3,27} Sedative effects appear to be minimal with fexofenadine, even when the drug was combined with alcohol.

The most commonly reported adverse effects with the second generation agents are headache, pharyngitis, dry mouth, and somnolence; however, the incidence of these effects generally does not differ from placebo except for somnolence with cetirizine, which is double the incidence seen in placebo groups.³ For desloratadine, the incidence of adverse effects (including somnolence) with a 5mg dose was similar to that seen with placebo.⁴

Mann and colleagues conducted a post-marketing surveillance study to determine the incidence of sedation with the non-sedating antihistamines.²⁸ Data were collected on 4 antihistamines — cetirizine, fexofenadine, loratadine, and acrivastine. Of the 3 antihistamines marketed in the US, cetirizine had the highest incidence of drowsiness or sedation (OR 3.53, 95% CI 2.07 to 5.42) followed by loratadine (OR 1, as comparator), and fexofenadine (OR 0.63, 95% CI 0.36 to 1.11). No significant difference was seen in the risk of sedation or drowsiness between loratadine and fexofenadine ($p=0.1$). The authors found no difference in the occurrence of accidents or injury between the 4 agents.

Salmun and colleagues conducted a prospective, randomized, double-blind trial to determine somnolence and motivation during the workday in patients taking antihistamines.²⁹ Sixty patients with allergic rhinitis were given either loratadine or cetirizine 10mg at 8AM daily for 7 days. Adverse effects, including somnolence and motivation, were graded 3 times daily using a visual analog scale (1=wide awake or fully motivated to 10=extremely somnolent or not motivated at all) and recorded in an electronic diary. Somnolence scores were similar between the 2 treatment groups at baseline and at 8AM; however, at 10AM, noon, and 3PM, somnolence scores were higher with cetirizine compared to loratadine ($p=.008$, $p=.001$, and $p<.001$, respectively). Similar results were seen for motivation scores.

In 2 randomized, cross-over studies of a total of 44 healthy volunteers, desloratadine 7.5mg did not significantly effect wakefulness or psychomotor performance compared to placebo.⁴⁴ In the same studies, diphenhydramine 50mg decreased wakefulness and impaired psychomotor performance significantly more than placebo or desloratadine ($p<0.01$). A randomized, placebo controlled crossover study of 18 healthy volunteers evaluated driving performance 2 and 3 hours after administration of desloratadine 5mg, diphenhydramine 50mg, and placebo.⁴⁵ Diphenhydramine significantly impaired brake reaction time ($p=0.001$ vs desloratadine) and the ability to maintain a steady lateral position ($p<0.0001$ vs desloratadine and placebo). Desloratadine did not differ from placebo on either of these measures.

Prolongation of the QT interval was reported with both astemizole and terfenadine and ultimately led to the withdrawal of these products from the US market. QT prolongation has subsequently been shown not to be a class effect of these agents and fexofenadine, loratadine, and cetirizine appear to have a very low potential for cardiotoxicity.³⁶ In 2 unpublished trials, desloratadine at a dose of 45mg/day for 10 days showed no significant effect on the QT interval in healthy volunteers.^{42,43}

VI. DRUG INTERACTIONS

As a class, antihistamines may interact with other drugs which cause CNS depression, such as alcohol, benzodiazepines, analgesics, and antidepressants, potentiating the sedative effects of antihistamines.³ However, such effects are less likely to be seen with the second generation antihistamines, due to their lesser sedative effects. According to one placebo-controlled randomized 4-way cross-over study in 25 healthy volunteers, desloratadine 7.5mg did not potentiate the effects of alcohol.⁵¹

The biggest concern regarding drug interactions with the second generation antihistamines is related to the cytochrome P450 (CYP450) enzyme system. Two second generation antihistamines—astemizole and terfenadine—were removed from the market due to serious, life-threatening QT prolongation resulting from drug interactions involving the cytochrome P450 enzyme system. To date, no significant cardiac effects have been reported with the available second generation antihistamines. A recent study evaluated the cardiovascular effects of fexofenadine in doses up to 240mg daily given in combination with

erythromycin or ketoconazole.³⁰ No increased incidence of adverse effects or QT prolongation were noted when fexofenadine was given in combination with these agents, although clinically and statistically significant increases in the fexofenadine C_{max} and AUC were seen (135% and 164%, respectively for ketoconazole; and, 82% and 109%, respectively for erythromycin).⁸ The mechanism for this interaction appears to be either enhanced GI absorption or decreased biliary excretion or GI secretion. Fexofenadine should also not be administered within 15 minutes of a magnesium and aluminum containing antacid, as the C_{max} and AUC of fexofenadine decrease by 43% and 41%, respectively.⁸ Additionally, in healthy volunteer studies assessing the drug and food interaction potential of fexofenadine and desloratadine, a significant increase in serum concentrations of fexofenadine was seen with azithromycin and a significant decrease was seen with grapefruit juice.^{49,50} No difference in the pharmacokinetics of desloratadine was seen with co-administration of either agent. Serum concentrations of loratadine are increased when administered concurrently with drugs that inhibit the CYP450 isoenzymes; erythromycin, ketoconazole, cimetidine.^{4,36} Although no adverse cardiac effects have been reported, there is potential for a higher risk of sedation. Cetirizine is primarily eliminated as unchanged drug in the urine and is unlikely to interact with CYP450 inhibitors or inducers.⁹ In fact, administration of cetirizine with erythromycin, azithromycin, or ketoconazole has been shown to produce no discernable change in electrocardiographic findings.^{33,34,35} No relevant interactions between desloratadine and erythromycin, fluoxetine, cimetidine, or ketoconazole have been documented.^{7,47,48}

VII. INDICATIONS/DOSING

The indications and recommended doses of the second generation antihistamines are given in Tables 7.

Table 7. Indications and Dosing of Second Generation Antihistamines^{3,4,31}

Agent	Indication	Dosage form	Usual dose
Loratadine	Relief of nasal/non-nasal sx's of SAR and for idiopathic urticaria in pts >6 YO.	Claritin tablets, syrup	Adults and children (>6 y): 10mg once daily; Hepatic/renal function impaired: 10mg every other day.
Loratadine w/pseudoephedrine	For relief of symptoms of seasonal allergic rhinitis.	Claritin-D 12 hour	Adults and adolescents (>12y): 1 tablet ever 12 h; Renal function impaired: 1 tablet daily; Contraindicated in pts with hepatic dysfunction.
		Claritin-D 24 hour	Adults and adolescents (>12y): 1 tablet daily; Renal function impaired: 1 tablet every other day; contraindicated in pts with hepatic dysfunction.
Desloratadine	For relief of nasal and non-nasal sx's of SAR and PAR in ps 12 years and >. For treatment of chronic idiopathic urticaria.	Clarinx tablets	Adults and adolescents (>12 y): 5mg once daily; 5mg every other day should be used in pts with hepatic dysfunction.
Fexofenadine	For relief of sx's of SAR (sneezing, rhinorrhea, itchy nose, palate and throat, and itchy watery, and red eyes). For tx of uncomplicated skin manifestations of chronic idiopathic urticaria.	Allegra capsules	Adults and adolescents (>12 y): 60mg 2x daily or 180mg daily; 60mg/day should be used in pts with impaired renal function. Children 6-11 years: 30mg 2x daily; 30mg/day should be used in pts with impaired renal function.
Fexofenadine w/pseudoephedrine	For relief of symptoms of SAR.	Allegra-D capsules	Adults & adolescent (>12y): 1 tablet 2x daily; 1 tablet/day should be used in pts w/impaired renal function.
Cetirizine	Relief of symptoms associated with seasonal/perennial allergic rhinitis and chronic idiopathic urticaria.	Zyrtec tablets and syrup	Adults and children (>6 y): 5 to 10mg once daily; Children 2-5 years: 2.5mg daily to max of 5mg daily or 2.5mg every 12 hrs. Hepatic/renal function impaired: 5mg 1x daily for adults & children >6 y. For children <6 y with hepatic/renal impairment, use of cetirizine is not recommended.
Cetirizine w/pseudoephedrine	For relief of symptoms of seasonal or perennial allergic rhinitis.	Zyrtec-D	Adults and children (>12 y): 1 tablet every 12 hours. Hepatic/renal function impaired: 1 tablet daily.

VIII. PHARMACOECONOMICS

A recent retrospective analysis of the costs associated with the use of second generation antihistamines for allergic rhinitis included an evaluation of loratadine, fexofenadine, cetirizine and nasal steroids.⁹¹ A total of 202,426 patients diagnosed with allergic rhinitis who had at least one prescription claim for an allergic rhinitis therapy were identified. Seventy-one percent of those patients had a claim for a second generation antihistamine. The most common regimen was monotherapy with loratadine in 28% of patients. The next most common regimen was combination therapy with loratadine and a nasal steroid in 20% of patients. Those patients with the highest severity index, as determined by the number of co-morbid conditions, were the most likely to receive combination therapy. The annual treatment charges for allergic rhinitis included inpatient, outpatient, ancillary, emergency, and drug costs. The mean annual treatment charge across all patients was \$465.21. The greatest departmental cost was pharmacy-related costs at an average of \$236.02 per year. There were differences found in the total costs among the regimens studied, with fexofenadine monotherapy or combination therapy with nasal steroids being significantly less costly than loratadine or cetirizine based regimens; however, the cost of the drug was the primary determinant of the total treatment costs.

IX. CONCLUSIONS

Overall, all of the second generation antihistamines appear to be effective in relieving symptoms of allergic rhinitis, with little differences seen in efficacy. To date, none of the currently available second generation agents have been reported to cause or be associated with serious adverse events. Unlike earlier second generation agents, QTc prolongation does not appear to be a concern with the currently available products.

Although there appears to be little difference in efficacy between agents, one large study between fexofenadine and loratadine found fexofenadine to have a greater effect on quality of life and on some allergy symptoms, such as itchy/watery/red eyes and nasal congestion. Loratadine has an indication for pediatrics and is available in a liquid formulation. It is also available as a rapidly disintegrating tablet. Fexofenadine is available for use in pediatrics, but only as a tablet. A liquid formulation is in development but an availability date is not known. Desloratadine is only available in a tablet formulation for children and adults 12 years of age and older. Development of a rapidly disintegrating tablet, a liquid, and a combination with pseudoephedrine is underway.

Unlike the other available second generation antihistamines, loratadine does undergo hepatic metabolism via the CYP450 enzyme system and is subject to drug interactions involving 3A4 inhibitors and inducers. Fexofenadine interacts with ketoconazole and erythromycin resulting in increased concentrations of fexofenadine. As per the precautions section of the package insert, there were no differences in adverse events or QTc intervals following coadministration of erythromycin or ketoconazole. It also interacts with magnesium and aluminum containing antacids and grapefruit juice resulting in a decrease in fexofenadine concentrations. Cetirizine and desloratadine do not appear to have any significant drug interactions.

As would be expected, addition of a nasal decongestant (pseudoephedrine) to any of the second generation antihistamines improved symptoms of nasal stuffiness; however, no difference was seen in other symptoms of allergic rhinitis in studies addressing combination therapy.

The long half-life of desloratadine has been cited as facilitating the product's ability to provide a full 24 hours of effect as compared to loratadine's shorter half-life; however, comparative data in patients with allergic disease does not exist. It has been suggested that desloratadine may offer therapeutic advantages over other non-sedating antihistamines for treatment of SAR due to its decongestant properties. There are no head-to-head studies to substantiate this claim. Furthermore, although there are unpublished trials demonstrating significant effects on nasal congestion with desloratadine versus placebo, in 3 out of the 4 multiple-dose clinical trials that were conducted for the FDA approval process, desloratadine failed to differentiate from placebo in the "nasal congestion/stuffiness" symptom score. Final determination of potential clinical advantages for desloratadine in terms of onset of effect, duration of effect, efficacy (especially nasal congestion scores), and quality of life compared to older second generation antihistamines awaits the performance of head-to-head trials of the products.

Based on the available data, there are no significant clinical or safety differentiating factors between desloratadine and the other non-sedating anti-histamines that would preclude OTC status for desloratadine. Since the FDA has already approved the status of loratadine as an OTC antihistamine, we recommend that desloratadine be converted to OTC status as soon as the FDA acquires adequate naturalistic studies for its use.

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