



Antihistamines, Minimally Sedating Therapeutic Class Review (TCR)

June 22, 2015

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Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
acrivastine/pseudoephedrine (Semprex D®) ¹	UCB	<ul style="list-style-type: none"> Relief of symptoms associated with seasonal allergic rhinitis (AR) in adults and children 12 years of age and older
cetirizine OTC (Zyrtec® OTC) ^{2,3}	generic McNeil Consumer	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies (sneezing; runny nose; itchy, watery eyes; itchy throat or nose) in adults and children 2 years of age and older Relief of symptoms associated with seasonal AR due to allergens such as ragweed, grass, and tree pollens in adults and children 2 years of age and older Relief of symptoms associated with perennial AR due to allergens such as dust mites, animal dander, and molds in adults and children 6 months of age and older Treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children 6 months of age and older
cetirizine ODT OTC (Zyrtec® Allergy ODT) ⁴	McNeil Consumer	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies (sneezing; runny nose; itchy, watery eyes; itchy throat or nose) in adults and children 6 years of age and older
cetirizine/pseudoephedrine OTC (Zyrtec-D® OTC 12 Hour) ⁵	generic McNeil Consumer	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms associated with seasonal or perennial AR in adults and children 12 years of age and older
desloratadine (Clarinet®, Clarinet Redi-Tabs®) ⁶	generic	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms of seasonal AR in patients 2 years of age and older Relief of nasal and non-nasal symptoms of perennial AR in patients 6 months of age and older Symptomatic relief of pruritus, reduction in the number of hives, and size of hives in patients with CIU 6 months of age and older
desloratadine/pseudoephedrine (Clarinet-D® 12-Hour) ⁷	Merck	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms of seasonal AR, including nasal congestion in adults and children 12 years of age and older
desloratadine/ pseudoephedrine (Clarinet-D® 24-Hour) ⁸	Merck	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms of seasonal AR, including nasal congestion in patients 12 years of age and older

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
fexofenadine OTC (Allegra®) ⁹	generic	<ul style="list-style-type: none"> Relief of symptoms of seasonal AR in patients 6 years of age and older Treatment of uncomplicated skin manifestations of CIU in adults and children 6 years of age and older
fexofenadine OTC (Allegra® Oral Suspension)	generic	<ul style="list-style-type: none"> Relief of symptoms of seasonal AR in children 2 years of age and older Treatment of uncomplicated skin manifestations of CIU in children ≥ 6 months to less than 12 years of age
fexofenadine orally disintegrating tablet OTC (Allegra ODT®) ¹⁰	generic	<ul style="list-style-type: none"> Treatment of symptoms related to seasonal AR and CIU in adults and children 6 years of age and older
fexofenadine/pseudoephedrine OTC (Allegra-D® 12 and 24 Hour) ^{11, 12}	generic	<ul style="list-style-type: none"> Relief of symptoms associated with seasonal AR in adults and children 12 years of age and older
levocetirizine (Xyzal®) ¹³	generic, Sanofi-Aventis	<ul style="list-style-type: none"> Relief of symptoms associated with seasonal AR in adults and children 2 years of age and older Relief of symptoms associated with perennial AR in adults and children 6 months of age and older Treatment of uncomplicated skin manifestations of CIU in adults and children 6 months of age and older
loratadine OTC (Alavert®, Claritin®, generic) ¹⁴	generic	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children 6 years of age and older (syrup for ages 2 years and older)
loratadine ODT OTC (Alavert Quick Dissolving, Claritin Redi-Tabs, generic) ¹⁵	generic	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children 6 years of age and older
loratadine OTC (Children’s Claritin® Chewable)	Schering-Plough Healthcare Products	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies in patients 2 years of age and older
loratadine OTC (Claritin® Liqui-Gels®)	Schering-Plough Healthcare Products	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children 6 years of age and older
loratadine/pseudoephedrine OTC (Alavert Allergy & Sinus, Claritin-D® 12 Hour, generic) ¹⁶	generic	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children 12 years of age and older
loratadine/pseudoephedrine OTC (Claritin-D 24 Hour, generic) ¹⁷	generic	<ul style="list-style-type: none"> Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children 12 years of age and older

The combination antihistamine/pseudoephedrine products have an additional indication of temporary reduction in swelling of nasal passages and temporary restoration of freer breathing through the nose.¹⁸

Cetirizine, loratadine, and fexofenadine are available over-the-counter (OTC) in various dosage forms.

OVERVIEW

Allergic Rhinitis (AR)

Rhinitis is defined as inflammation of the membranes lining the nose and is characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage. Although rhinitis may be caused by non-allergic (infectious, hormonal, occupational) factors, allergic rhinitis (AR) is the most common form.¹⁹

AR is characterized by inflammation of the nasal mucous membranes due to an allergic response. As a result, most patients with AR experience nasal congestion. However, nasal congestion is also present in common chronic rhinosinusitis. An important distinguishing feature of AR is concomitant clear rhinorrhea and frequent sneezing. Ocular irritation or burning is nearly exclusive to AR. Mucoid postnasal discharge in the posterior pharynx is also indicative of AR.

There are two common forms of AR: seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). SAR occurs when plant pollens are at their highest levels in spring, summer, and early fall. PAR occurs year-round and is usually caused by home or workplace pollutants. Individuals may have one or both forms of allergic rhinitis. Accordingly, the 2008 updated guidelines from the American Academy of Allergy, Asthma and Immunology (AAAAI) on the diagnosis and management of rhinitis introduced for the first time the classification of episodic allergic rhinitis.²⁰ Episodic allergic rhinitis is neither seasonal nor perennial, but is triggered by sporadic exposure to inhalant aeroallergens.

Estimates from 2008 suggest 10 to 30% of adults and up to 40% of children experience allergic rhinitis.^{21,22} The cost of treating allergic rhinitis almost doubled from 2000 to 2005 from \$6.1 billion to \$11.2 billion. More than half of the costs were related to prescription medications.²³ AR is the number one cause for work absenteeism. In children, approximately two million school days per year are lost due to allergic rhinitis.²⁴

Avoidance of allergens is fundamental to the management of AR. An effort to alter the home and work environments is crucial, and in perennial allergies (e.g., dust and mold), allergen avoidance is the cornerstone of treatment. Patients with seasonal allergies (e.g., trees, weeds, etc.) experience difficulty avoiding common allergens during certain times each year. Initiation of treatment one to two weeks preceding onset of a budding season will often result in more effective reduction of symptoms.

Intranasal corticosteroids and oral antihistamines are the primary treatment options for AR.²⁵ Alternative agents, such as leukotriene modifiers, cromolyn sodium, and antihistamine nasal sprays, may be appropriate in some patients.

Intranasal corticosteroids are most effective in controlling symptoms of AR.²⁶ The agents are highly effective in relieving nasal allergy symptoms (e.g., congestion, sneezing, runny nose).

Oral antihistamines are particularly effective in severe rhinorrhea, sneezing, pruritus, and conjunctivitis associated with AR, although less effective for nasal congestion. The usefulness of first-generation (sedating) antihistamines is reduced because the agents may produce significant sedation, performance impairment, and/or anticholinergic effects. Consequently, the second-generation (minimally sedating) antihistamines, associated with a lower incidence of side effects, are generally considered before sedating antihistamines, especially in adults and school-age children. For patients with more significant nasal congestion, several of the minimally sedating antihistamines are available as combination dosage forms with pseudoephedrine, a decongestant.

The 2008 updated guidelines from the American Academy of Allergy, Asthma and Immunology (AAAAI) discuss developments in the management of AR.²⁷ The guidelines recognize the importance of pulmonary function testing, particularly in patients with comorbidities including asthma, sinusitis, and sleep apnea. Advantages and disadvantages of single and combination therapies of medications released in the last ten years are discussed. Consideration of using a rhinitis action plan is advocated. Charts are included to assist physicians in assessing symptoms severity and establishing a treatment plan. The role of each therapeutic class is summarized, and oral antihistamines are considered most effective for treatment for seasonal and perennial AR when used continuously. Due to rapid onset of action, antihistamines, dosed when needed, can be an appropriate treatment option for episodic AR. Oral antihistamines are as effective as intranasal corticosteroids for the treatment of ocular symptoms but are less effective than intranasal corticosteroids for nasal congestion and allergic rhinitis symptoms. Second generation antihistamines are preferred over the first generation agents due to more favorable side effect profile (less sedation and fewer anticholinergic side effects), as well as a safer option for use in pregnancy. Oral decongestants are not recommended in children younger than four years of age.²⁸

Chronic Idiopathic Urticaria (CIU)

Urticaria is defined as the transient appearance of elevated, erythematous pruritic wheals (hives). The condition commonly affects the trunk and extremities, sparing the palms and soles, but urticaria may affect any epidermal or mucosal surface. Urticaria is predominantly due to release of mast cell mediators, mainly histamine, as a result of an ongoing immediate hypersensitivity reaction. Chronic idiopathic urticaria (CIU), where disease activity continues for more than six weeks, is common, comprising 70% of all cases.²⁹ Chronic idiopathic urticaria can occur at any age; however, CIU is most common in young adults. In most patients, the lesions clear spontaneously or respond rapidly to treatment with antihistamines; however, some patients continue to have lesions for prolonged periods. Of patients with CIU and angioedema, 75% have symptoms for longer than one year, 50% have symptoms for longer than five years, and 20% have symptoms for decades.

When attempts at identifying the cause of urticaria have failed (thus eliminating the possibility of reducing exposure), the patient requires treatment. Minimally-sedating H₁-receptor antagonists represent the basic therapy for all CIU patients. Older sedating antihistamines, such as hydroxyzine and diphenhydramine, may be indicated if symptoms are severe, are associated with angioedema, and if the patient is anxious and/or disturbed at night.³⁰ If clinical response is not adequate, H₂-inhibitory drugs may be added to the antihistamine.³¹ Other agents reported to be beneficial in some cases include doxepin, a tricyclic antidepressant with anti-H₁ and anti-H₂ properties, and the leukotriene receptor antagonists. If all agents fail, a course of glucocorticoids may be required. Third-line therapies involving immunosuppressive agents are only appropriate for patients with CIU refractory to other measures.³²

All of the minimally sedating antihistamines are effective treatments for CIU.^{33,34,35,36} Little comparative data regarding the use of these agents in CIU are available; therefore, the focus of this review is AR.

PHARMACOLOGY

Minimally sedating antihistamines are selective, competitive, peripherally-acting histamine H₁-receptor antagonists with little or no central or autonomic nervous system activity.^{37,38}

PHARMACOKINETICS³⁹

Drug (Metabolite)	t _{max} (hr)	t _{1/2} (hr)	Protein Binding (%)	Excretion (%)	Onset of Action (hr)	Duration of Action (hr)
acrivastine (Semprex-D) ⁴⁰ (1 metabolite)	1.14 ± 0.23	1.9 ± 0.3 (3.8 ± 1.4 0)	50 ± 2.0	Urine: 84 Feces: 13	1	12
cetirizine (Zyrtec) ^{41,42} (1 metabolite)	1	8.3	93	Urine: 50 Feces: 10	0.3-1	≥ 24
desloratadine (Clarinex) ^{43,44} (6 metabolites)	3	27	82-87	--	1	24
fexofenadine (Allegra) ^{45,46} (no metabolites)	2.6	14.4	60–70	Urine: 11 Feces: 80	1	>12
fexofenadine ODT (Allegra ODT) ⁴⁷ (no metabolites)	2	14.4	60–70	Urine: 11 Feces: 80	1	>12
levocetirizine (Xyzal) ⁴⁸ (4 metabolites)	0.9	8-9	91-92	Urine: 85 Feces: 13	1	24
loratadine ⁴⁹ (12 metabolites, including desloratadine)	1.2 ± 0.3 (1.5 ± 0.7)	7.8 ± 4.2 (24 ± 9.8)	98 (73–76)	Trace	3-4	24

Results are mean ± standard deviation.

t_{max} = time from oral intake to peak plasma drug concentration; t_{1/2} = elimination half-life

CONTRAINDICATIONS/WARNINGS^{50,51,52,53,54,55,56}

Pseudoephedrine, the decongestant component of Allegra-D, Claritin-D, Clarinex-D, Zyrtec-D, and Semprex D, is contraindicated in patients with narrow-angle glaucoma, urinary retention, severe hypertension, severe coronary artery disease, and in patients who take monoamine oxidase (MAO) inhibitors or have recently (prior two weeks) discontinued a MAO inhibitor. In addition to these contraindications, pseudoephedrine should be carefully monitored in patients with hyperthyroidism, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, or renal impairment. The antihypertensive effects of some medications (including beta-adrenergic blockers) may be reduced by pseudoephedrine. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digoxin. Pseudoephedrine has also been associated with adverse effects, such as insomnia, tremor, and arrhythmias. Furthermore, pseudoephedrine has been associated with CNS over stimulation associated with convulsions, and may eventually lead to hypotension with cardiovascular collapse. Additionally, there are post-marketing reports on desloratadine (Clarinex) as a single agent and in combination with pseudoephedrine (Clarinex-D) for tachycardia and movement disorders including extrapyramidal and dystonia symptoms.^{57,58} It should also be noted that levocetirizine (Xyzal) is contraindicated in children ages six to 11 years of age with renal impairment and in patients with end stage renal disease with a creatinine clearance (CrCl) less than 10 mL/min or undergoing hemodialysis.⁵⁹ Levocetirizine has a warning of urinary retention associated with levocetirizine usage in post-marketing studies. Levocetirizine should be used with caution in patients at greater risk for urinary retention, such as those with spinal cord injuries and prostatic hyperplasia. Furthermore, if urinary retention is discovered, levocetirizine should be discontinued immediately.

Fexofenadine orally-disintegrating tablets (Allegra ODT) contain phenylalanine, a component of aspartame. This formulation is not recommended for use in patients with phenylketonuria.

The other agents do not have specific contraindications. However, cautious use in patients with renal impairment, as well as geriatric patients, is recommended. Cetirizine is contraindicated in those patients with a known hypersensitivity to it, any of its ingredients, or hydroxyzine.

DRUG INTERACTIONS

Drug	azithromycin	erythromycin	Grapefruit juice*	ketoconazole	theophylline	Al and Mg containing antacids
acrivastine (Semprex D) ⁶⁰	--	--	--	--	--	--
cetirizine (Zyrtec) ⁶¹	--	--	--	--	16% decrease in cetirizine clearance	--
desloratadine (Clarinet) ^{62,63,64}	15% increase in desloratadine C _{max} 15% increase in major metabolite C _{max}	24% increase in desloratadine C _{max} 43% increase in major metabolite C _{max}	--	45% increase in desloratadine C _{max} 43% increase in major metabolite C _{max}	--	--
fexofenadine* (Allegra) ^{65,66,67}	69% increase in fexofenadine C _{max}	82% increase in fexofenadine C _{max}	36% decrease in fexofenadine bioavailability	135% increase in fexofenadine C _{max}	--	43% decrease in fexofenadine C _{max} when given within 15 minutes
levocetirizine (Xyzal) ⁶⁸	--	--	--	--	--	--
loratadine (Claritin) ⁶⁹	--	increase in loratadine levels	--	increase in loratadine levels	--	--

*In addition to grapefruit juice, other fruit juices such as orange or apple juice, may decrease the bioavailability of fexofenadine. Clinical studies indicate a decrease in efficacy in the treatment of urticaria when fexofenadine is administered with orange or grapefruit juice.

ADVERSE EFFECTS

Adults

Drug	Dry mouth	Dyspepsia	Fatigue	Headache	Insomnia	Nausea	Somnolence
acrivastine/ pseudoephedrine (Semprex D) ⁷⁰	7	2	nr	19	4	2	12
cetirizine (Zyrtec) ⁷¹	5	<2	5.9	>2	<2	>2	11-14
cetirizine/pseudoephedrine (Zyrtec D) ⁷²	3.6	reported	2.4	reported	4	reported	1.9
desloratadine (Clarinet) ⁷³	3	3	2.1-5	14	nr	5	2.1
desloratadine/ pseudoephedrine (Clarinet-D 12-Hour) ⁷⁴	8	nr	4	8	10	2	3
desloratadine/ pseudoephedrine (Clarinet-D 24-Hour) ⁷⁵	8	nr	3	6	5	2	3
fexofenadine (Allegra) ⁷⁶	nr	1.3	1.3	10.6	<1	1.6	1.3-2.2
fexofenadine/ pseudoephedrine (Allegra-D 12-hour) ⁷⁷	2.8	2.8	nr	13	12.6	7.4	nr
levocetirizine (Xyzal) ⁷⁸	2-3	nr	1-4	nr	nr	nr	5-6
loratadine (Claritin) ⁷⁹	2-4	2-3	4-6	12-18	1-4	2	4-8
loratadine/ pseudoephedrine 12 hr (Claritin D-12 hr) ⁸⁰	14	3	4	19	16	3	7
loratadine/ pseudoephedrine 24 hr (Claritin D-24 hr) ⁸¹	8	nr	3	nr	5	3	6

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Children

Drug	Abdominal Pain	Cough	Fatigue	Nausea	Pharyngitis	Somnolence	Headache
cetirizine (Zyrtec) ⁸²	4.4-5.6	2.8-4.4	nr	1.9-2.8	2.8-6.2	1.9-4.2	11-14
desloratadine (Clarinet) ⁸³	nr	10.8	5	3-5	3-4.5	9.1	14
fexofenadine (Allegra) ⁸⁴	nr	3.8	nr	nr	nr	nr	7.2
levocetirizine (Xyzal) ⁸⁵	nr	3	nr	nr	nr	3	nr
loratadine (Claritin) ⁸⁶	2	4	3	nr	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Somnolence

A literature search (MEDLINE and cross-references) was performed using the keywords driving and antihistamine.⁸⁷ Sixteen studies using the on-the-road driving test during normal traffic were included in the review. Studies were double-blinded and placebo-controlled and included a positive control. First-generation antihistamines (diphenhydramine, triprolidine, terfenadine, d-chlorpheniramine, clemastine) significantly impair driving performance after both one-time and repeated (daily) administration. Second-generation antihistamines (cetirizine, loratadine, and acrivastine) may also impair driving performance, but the magnitude and extent of impairment depend on the administered dose, sex, and time between testing and treatment administration. Tolerance develops after four to five days of administration, but impairment is not absent. The third-generation antihistamine (fexofenadine) produced no driving impairment after both one-time and repeated administration.

loratadine (Claritin) versus fexofenadine (Allegra) versus cetirizine (Zyrtec)

Post-marketing reports of sedation or drowsiness were obtained for a total of 43,363 patients receiving loratadine, fexofenadine, or cetirizine.⁸⁸ Compared with loratadine, the odds ratios (adjusted for age and sex) for the incidence of sedation were 0.63 (p=0.1) for fexofenadine and 3.53 (p<0.0001) for cetirizine. No increased risk of accident or injury was evident with any of the drugs. These data indicate that fexofenadine and loratadine may be more appropriate than cetirizine for people working in safety-critical jobs.

loratadine (Claritin) versus cetirizine (Zyrtec)

A double-blind study compared the somnolence and motivation profiles of loratadine and cetirizine in 60 patients.⁸⁹ In the study, patients aged 12 years and older and actively exhibiting symptoms of AR were randomized to receive loratadine 10 mg or cetirizine 10 mg daily at 8:00 a.m. for one week. After patients took the medication, somnolence and degree of motivation to perform activities were recorded in an electronic diary using a visual analog scale at four times during the workday (8:00 a.m., 10:00 a.m., 12:00 p.m., and 3:00 p.m.). A statistically significant difference in somnolence scores between the loratadine and cetirizine groups at 10:00 a.m. (p=0.008), 12:00 p.m. (p=0.001), and

3:00 p.m. ($p < 0.001$), with the cetirizine group showing a greater degree of somnolence, was reported. Likewise, statistically significant differences in motivation scores between the loratadine and cetirizine groups at 10:00 a.m. ($p = 0.014$), 12:00 p.m. ($p = 0.001$), and 3:00 p.m. ($p < 0.001$) were reported, indicating patients taking loratadine were comparatively more motivated during the workday. The results of the study demonstrate, in patients who have AR, cetirizine use promotes somnolence and decreases motivation to perform activities during the workday compared with loratadine.

desloratadine (Clarinet) versus diphenhydramine (Benadryl)

One randomized, double-blind, three-way, crossover study conducted in Europe evaluated the effect of a single dose of desloratadine 5 mg, diphenhydramine 50 mg, or placebo on standard over-the-road driving tests ($n = 18$).⁹⁰ No significant differences were noted between desloratadine and placebo in standard deviation of lateral position (SDLP), whereas diphenhydramine treatment significantly increased SDLP ($p < 0.001$ for both comparisons). Brake reaction time was significantly faster following treatment with desloratadine than diphenhydramine (473.72 ms versus 541.22 ms; $p < 0.001$) or placebo (512.06 ms; $p = 0.033$). The majority of performance tests showed no significant differences among groups.

SPECIAL POPULATIONS^{91,92,93,94,95,96,97,98,99,100,101,102,103,104}

Pediatrics

Safety and effectiveness of acrivastine/pseudoephedrine (Semprex-D) in pediatric patients under the age of 12 years have not been established.

Safety and effectiveness of levocetirizine (Xyzal) in pediatric patients under six months of age have not been established. The recommended doses for children ages six months to 11 years should not be exceeded.

Safety and effectiveness of fexofenadine (Allegra) in pediatric patients have been established in ages two years and older for the liquid formulation. However, use of fexofenadine for the CIU indication for patients less than six years of age requires physician evaluation/prescription. Physician oversight of fexofenadine therapy is recommended for patients age six months to 23 months of age. Children's Allegra ODT and oral tablets are approved in ages two years and older.

A multicenter, double-blind, randomized, placebo-controlled, parallel-group, two-week trial was conducted in 453 preschool children ages two to five years old with allergic rhinitis to compare the safety and tolerability of twice daily fexofenadine (Allegra) 30 mg versus placebo.¹⁰⁵ To facilitate dosing, capsule contents were mixed with applesauce. Safety assessments included physical examination, laboratory testing, 12-lead electrocardiography, vital signs and adverse event reporting. Treatment emergent adverse effects were observed in 116 of the 231 participants who received placebo. Of patients receiving fexofenadine, 111 of the 222 participants had treatment emergent adverse effects. Nineteen of the 116 participants (8.2%) and 21 of the 111 participants (9.5%) were determined to have a potential link to the study medication, placebo or fexofenadine, respectively. No clinically relevant differences were noted in any of the other safety parameters under study. The findings suggest fexofenadine is well tolerated in children ages two to five years of age with allergic rhinitis.

Safety and effectiveness of desloratadine (Clarinet) and cetirizine (Zyrtec) in pediatric patients under six months of age have not been established.

Safety and effectiveness of loratadine (Claritin) in pediatric patients under two years of age have not been established.

Combination products containing pseudoephedrine in excess of 60 mg daily should not be used in children under 12 years of age.

Pregnancy

No adequate, well-controlled studies have been conducted in pregnant women. All agents should be used only if clearly needed during pregnancy. Cetirizine (Zyrtec), acrivastine (Semprex D), levocetirizine (Xyzal), and loratadine (Claritin) are Pregnancy Category B. Desloratadine (Clarinex), cetirizine/pseudoephedrine (Zyrtec D), and fexofenadine/fexofenadine ODT (Allegra, Allegra ODT) are Pregnancy Category C.

Hepatic Impairment

A 50% reduction in dosage or dosage frequency is recommended for cetirizine (Zyrtec), desloratadine (Clarinex), and loratadine (Claritin). Use of cetirizine in children less than six years of age with impaired renal or hepatic function is not recommended. Patients with hepatic impairment did not demonstrate any differences from healthy patients when using fexofenadine or fexofenadine ODT (Allegra, Allegra ODT). Consult product labeling.

Renal Impairment

A 50% reduction in dosage or dosage frequency is recommended for cetirizine (Zyrtec), desloratadine (Clarinex), fexofenadine/fexofenadine ODT (Allegra, Allegra ODT), and loratadine (Claritin) with renal impairment. Acrivastine/pseudoephedrine (Semprex-D) is not recommended for use in patients with creatinine clearance (CrCl) \leq 48 mL/min. Patients with renal impairment demonstrated higher plasma levels of fexofenadine (Allegra), as well as longer elimination half lives than observed in healthy volunteers. Levocetirizine (Xyzal) requires a dosage adjustment in the renally impaired. Consult product labeling.

Race and Gender

No studies have been done to determine the effect of race on the pharmacokinetics of desloratadine (Clarinex). In addition, there have been no clinically significant gender-related differences noted with the use of desloratadine (Clarinex).

Age

A dosing adjustment of cetirizine (Zyrtec) may be necessary in patients 77 years of age and older.

DOSAGES

Drug	Adult Dose (including children 12 years and older)	Pediatric Dose	Availability
acrivastine/pseudoephedrine (Semprex D) ¹⁰⁶	1 capsule 4 times daily	--	8 mg acrivastine/60 mg pseudoephedrine capsules
cetirizine OTC (Zyrtec, Zyrtec ODT) ¹⁰⁷	5 or 10 mg daily 65 yrs and older: 5 mg daily	6 – 11 yrs: 5 or 10 mg daily 2 – 5 yrs: 2.5 – 5 mg (½ – 1 tsp or 5 mg chewable tab) daily 6 – 23 mo: 2.5 mg (½ tsp) daily 12 – 23 mo: may increase to 2.5 mg (½ tsp) every 12 hours	5 mg and 10 mg tablets 5 mg and 10 mg chewable tablets 1 mg/mL syrup 10 mg orally disintegrating tablets
cetirizine/pseudoephedrine OTC (Zyrtec-D 12 Hour) ¹⁰⁸	1 tablet twice daily	--	5 mg cetirizine/120 mg pseudoephedrine extended-release (12 hour) tablets
desloratadine (Clarinet, Clarinet Redi-Tabs) ¹⁰⁹	5 mg daily	6 – 11 yrs: 2.5 mg (1 tsp) daily 12 mo – 5 yrs: 1.25 mg (½ tsp) daily 6 – 11 mo: 1 mg (2 mL) daily	5 mg tablets 0.5 mg/mL syrup 2.5 mg and 5 mg orally disintegrating tablets
desloratadine/ pseudoephedrine (Clarinet-D 12-Hour) ¹¹⁰	1 tablet every 12 hours	--	2.5 mg desloratadine/120 mg pseudoephedrine extended-release (12 hour) tablets
desloratadine/ pseudoephedrine (Clarinet-D 24-Hour) ¹¹¹	1 tablet daily	--	5 mg desloratadine/240 mg pseudoephedrine extended-release (24 hour) tablets
fexofenadine OTC (Allegra) ¹¹²	60 mg twice daily or 180 mg daily	6 – 11 yrs: 30 mg twice daily	30 mg, 60 mg, and 180 mg tablets

Dosages (continued)

Drug	Adult Dose (including children 12 years and older)	Pediatric Dose	Availability
fexofenadine OTC (Allegra Oral Suspension)* ¹¹³	60 mg (2 tsp) twice daily	<p>2 yrs – 11 yrs: 30 mg (1 tsp) twice daily. Decrease dose to 30 mg (1 tsp) once daily in cases of poor renal function.</p> <p>6 mo – 23 mo: 15 mg (½ tsp) twice daily Decrease dose to 15 mg (½ tsp) once daily in cases of poor renal function.</p>	6 mg/mL oral suspension
fexofenadine ODT OTC (Allegra ODT) ¹¹⁴	60 mg twice daily	<p>6 – 11 yrs: 30 mg twice daily on an empty stomach</p>	30 mg orally disintegrating tablet
fexofenadine/ pseudoephedrine OTC (Allegra-D 12 hour) ¹¹⁵	1 tablet twice daily	--	60 mg fexofenadine/120 mg pseudoephedrine extended-release (12 hour) tablets
fexofenadine/ pseudoephedrine OTC (Allegra-D 24 hour) ¹¹⁶	1 tablet once a day on an empty stomach (ages 12 years and older)	--	180 mg fexofenadine/240 mg pseudoephedrine extended-release (24 hour) tablets
levocetirizine (Xyzal) ¹¹⁷	5 mg once daily in the evening	<p>6 – 11 yrs: 2.5 mg (1 tsp) once daily in the evening</p> <p>6 months – 5 yrs: 1.25 mg (½ tsp) once daily in the evening</p>	<p>5 mg tablets</p> <p>2.5 mg/5 mL oral solution</p>
loratadine OTC (Claritin) ^{118,119}	10 mg daily	<p>6 – 11 yrs: 10 mg (2 tsp) daily</p> <p>2 – 5 yrs: 5 mg (1 tsp) daily</p>	<p>10 mg tablets</p> <p>10 mg orally disintegrating tablets</p> <p>1 mg/mL syrup</p> <p>10 mg orally disintegrating tablets for children</p> <p>10 mg liquid filled capsules</p>
loratadine chewable OTC (Children’s Claritin) ¹²⁰	10 mg (2 chew tablets) daily	<p>6 – 11 yrs: 10 mg (2 chew tablets) daily</p> <p>2 – 5 yrs: 5 mg (1 chew tablet) daily</p>	5 mg chewable tablets

Dosages (continued)

Drug	Adult Dose (including children 12 years and older)	Pediatric Dose	Availability
loratadine/ pseudoephedrine 12 hr OTC ¹²¹	1 tablet twice daily	--	5 mg loratadine/120 mg pseudoephedrine extended-release (12 hour) tablets
loratadine/ pseudoephedrine 24 hr OTC ¹²²	1 tablet daily	--	10 mg loratadine/240 mg pseudoephedrine extended-release (24 hour) tablets

Cetirizine, loratadine, and fexofenadine are available over-the-counter (OTC) in various dosage forms. All combination products containing pseudoephedrine are available without a prescription behind the pharmacy counter.

* Allegra allergy oral suspension, approved for the treatment of CIU in children 6 months to 11 years of age, is only available as OTC; however, for the treatment of chronic idiopathic urticaria (CIU), in children six months to less than six years of age, it requires evaluation by a physician and a prescription.¹²³ Dosing recommendation is based on previously recommended prescription suspension data (six months to younger than two years of age: 15 mg [2.5 mL of oral suspension] twice daily).

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in the category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Allergic Rhinitis

cetirizine (Zyrtec) versus fexofenadine (Allegra)

A study compared the duration of effect and efficacy of cetirizine 10 mg, fexofenadine 180 mg, and placebo in allergic subjects (n=575) exposed to pollen in the environmental exposure unit.¹²⁴ Patients were exposed to ragweed pollen for two days and randomized in a double-blind fashion to once-daily cetirizine 10 mg, fexofenadine 180 mg, or placebo. The total symptom severity complex score (TSSC) is the sum of the severity ratings (0=absent to 3=severe) of several self-rated symptoms including runny nose, sneezing, itchy nose/palate/throat, and itchy/watery eyes. Treatment evaluation was divided into three periods: period one (TSSC zero to five hours after the first dose), period two (TSSC 21-24 hours after the first dose), and period three (TSSC zero to two hours after the second dose). The onset of action was comparable, and similar efficacy was observed in period one for both active treatments.

For period two, the reduction in baseline was greater for cetirizine (-3.6) compared with fexofenadine (-2.7; $p < 0.001$) and placebo (-2; $p < 0.001$), representing a 33% greater reduction for cetirizine versus fexofenadine. For period three, cetirizine also reduced TSSC to a greater extent, as compared to fexofenadine (-5.2 versus -4.6; $p = 0.017$) and placebo (-3.9; $p < 0.001$). Treatment-related adverse events were similar in all groups with an incidence of somnolence of 1.3% for both active medications.

Another randomized, double-blind study of 599 patients compared the response to treatment between single doses of cetirizine 10 mg, fexofenadine 180 mg, and placebo at five to 12 hours after pollen exposure in an environmental exposure unit.¹²⁵ The primary efficacy endpoint was the change in TSSC score at 12 hours post dose. Cetirizine produced a 26% greater reduction in TSSC at 12 hours (-4.3 versus -3.4; $p = 0.001$) and a 14% greater reduction overall (-5 versus -4.4; $p < 0.001$) than fexofenadine. The incidence of treatment-emergent adverse events and somnolence was similar among all three groups.

In a multicenter, double-blind study, 821 patients were enrolled to receive fexofenadine 120 mg or 180 mg once daily, cetirizine 10 mg once daily, or placebo for two weeks for the treatment of seasonal allergic rhinitis (SAR).¹²⁶ The total symptom score (TSS) was calculated for four individual symptoms: sneezing, rhinorrhea, itchy nose, palate or throat, and itchy, watery, or red eyes. There were no differences in efficacy between the two doses of fexofenadine or between either dose of fexofenadine and cetirizine. The combined incidence of drowsiness or fatigue was greater with cetirizine (9%) than with placebo (4%) or fexofenadine (4%).

In a two-week, double-blind, randomized study, 495 subjects with moderate to severe SAR received fexofenadine 180 mg or cetirizine 10 mg once daily without regard to food intake to compare effects on symptoms, drowsiness, and motivation.¹²⁷ Improvement in daily 12-hour reflective and instantaneous individual symptoms and total symptom score (TSS) were statistically equivalent between the two treatment groups. As measured by visual analog scores, patients receiving fexofenadine experienced significantly less overall drowsiness compared to baseline than those receiving cetirizine ($p = 0.011$). Although there was a trend toward greater improvements in overall motivation with fexofenadine compared with cetirizine ($p = 0.0504$), improvements in overall motivation were statistically equivalent.

cetirizine (Zyrtec) versus loratadine (Claritin)

In a randomized, double-blind trial using an environmental exposure unit, cetirizine and loratadine were compared to placebo in 360 patients.¹²⁸ Subjects were randomized to two days at the environmental exposure unit (six to seven hours daily) along with administration of one of the two active treatments or placebo. Evaluation of symptom scores indicated onset of action was earlier with cetirizine 10 mg (one hour, $p \leq 0.001$) than with loratadine 10 mg (three hours, $p \leq 0.01$). Cetirizine produced a 25.4% reduction in symptom scores overall versus an 11.2% decrease with loratadine ($p = 0.006$) and a 4.8% increase with placebo ($p < 0.001$). Loratadine was also significantly more effective than placebo ($p = 0.002$). Cetirizine reduced symptom scores after the first dose versus placebo ($p \leq 0.001$) and at most time points versus loratadine ($p \leq 0.05$). Adverse events were reported in 1.7% of patients in each active-treatment group and in 2.5% in the placebo group.

A double-blind study was performed to evaluate the effectiveness of cetirizine and loratadine versus placebo in patients with AR.¹²⁹ Ninety patients with moderate to severe AR were given cetirizine 10 mg, loratadine 10 mg, or placebo daily for four weeks. The investigators demonstrated antihistamines showed good effectiveness in patients with AR as determined by rhinomanometry and by symptom

score versus placebo. In addition, cetirizine performed better in comparison to loratadine versus placebo.

In a double-blind study, 80 children (two to six years of age) with PAR were randomized to receive cetirizine or loratadine 0.2 mg/kg once daily for twenty-eight days.¹³⁰ According to patients' daily diary assessments, cetirizine was more effective than loratadine in relieving the symptoms of rhinorrhea, sneezing, nasal obstruction, and nasal pruritus. Both treatments were well tolerated.

desloratadine (Clarinet) versus fexofenadine (Allegra)

Forty-nine patients with SAR were randomized into a double-blind, placebo-controlled cross-over study during the grass pollen season, comparing two weeks of treatment with fexofenadine 180 mg or desloratadine 5 mg taken once daily in the morning.¹³¹ Measurements were made for peak nasal inspiratory flow (PNIF), the primary outcome variable, as well as nasal and eye symptoms. There were significant ($p < 0.05$) improvements, compared to placebo, with fexofenadine and desloratadine for PNIF, nasal blockage, nasal irritation, and total nasal symptoms, but not nasal discharge or eye symptoms. There were no significant differences between active treatments.

fexofenadine (Allegra) versus loratadine (Claritin)

A double-blind, two-phase, multicenter study was conducted to compare therapeutic responses to loratadine and fexofenadine in patients who failed initial therapy with the other drug.¹³² In the study, 661 patients were randomized to receive loratadine 10 mg once daily or fexofenadine 60 mg twice daily for 14 days (phase one); non-responders subsequently received the alternate medication for 14 days (phase two). Mean decreases in TSS were significantly greater with loratadine than with fexofenadine for the patients who completed phase one (-12.7 versus -10.2, respectively; $p = 0.019$) and for the patients who responded to initial therapy (-6.6 versus -6.1, respectively; $p = 0.037$). Of the 389 patients who responded to initial therapy, 61% had received loratadine and 57% had received fexofenadine. More non-responders to initial therapy had moderate, marked, or complete relief of symptoms after switching to loratadine than after switching to fexofenadine (62.4% versus 51.2%, respectively; $p = 0.005$). Overall, loratadine provided significantly better therapeutic response than fexofenadine in patients who failed to respond to initial therapy with the other drug.

A double-blind study compared the efficacy, safety, and impact on quality of life (QoL) of fexofenadine, loratadine, and placebo in patients with SAR.¹³³ In the study, 688 patients were randomized to receive fexofenadine 120 mg, loratadine 10 mg, or placebo daily for two weeks. Although both agents were more effective than placebo in reducing individual symptom scores, fexofenadine was significantly better than loratadine in improving itchy, watery, red eyes, as well as in relieving nasal congestion ($p \leq 0.05$ for both symptoms). Fexofenadine was also significantly better than loratadine ($p \leq 0.03$) and placebo ($p \leq 0.005$) in improving QoL; the differences were of a magnitude considered to be clinically relevant. Loratadine had no statistically significant effect on QoL compared with placebo. The incidence of adverse events was low and similar across all treatment groups.

To compare loratadine with fexofenadine and placebo in relieving symptoms of spring/summer SAR, investigators performed a double-blind study in patients aged 12 to 60 years.¹³⁴ Patients were randomized to loratadine 10 mg once daily, fexofenadine 60 mg twice daily, or matching placebo for seven days. Overall, administration of either loratadine or fexofenadine provided similar reductions from baseline TSS compared to placebo. Median time to 25% reduction and maximum reduction in morning TSS occurred significantly earlier in patients receiving loratadine. At the initial assessment

following the first dose, loratadine demonstrated a significant reduction from baseline in symptoms compared with fexofenadine. Time-to-event analysis indicated that a more significant reduction in symptoms occurs earlier with loratadine than with fexofenadine.

levocetirizine (Xyzal) versus placebo

Six placebo-controlled, randomized, double-blind controlled trials with 2,412 patients (265 patients between the ages of 12 to 17) were conducted to determine the efficacy of levocetirizine in management of symptoms associated with seasonal and perennial allergic rhinitis.¹³⁵ Efficacy was assessed using a TSS from patient recording of four or five symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, and/or ocular pruritus). Patients recorded daily symptoms using a 0-3 categorical severity scale (0=absent, 1=mild, 2=moderate, and 3=severe). One of the studies allowed recording of symptoms in an instantaneous manner one hour prior to the next dose. The primary endpoint was the mean TSS averaged over the first week then over the first two weeks for seasonal AR trials, and four weeks for perennial AR trials. Total symptom scores were significantly reduced in the active treatment groups in both seasonal and perennial AR trials ($p<0.001$).

A multicenter, double-blind, randomized controlled trial with 577 patients was conducted to determine the efficacy and safety of levocetirizine in improving symptoms and health-related quality of life in adults in the United States with SAR.¹³⁶ Patients were randomized to receive levocetirizine 5 mg or placebo once daily in the evening for two weeks. The primary endpoint was the 24-hour reflective Total Five-Symptom Score (T5SS; sum of rhinorrhea, sneezing, nasal congestion, and nasal and ocular pruritus) during the entire treatment period. Secondary assessments included the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) questionnaire, and Epworth Sleepiness Scale (ESS), each assessed at week one, week two, and the end of treatment. Levocetirizine resulted in significantly greater improvement from baseline versus placebo in the T5SS ($p<0.001$), overall RQLQ score ($p<0.001$), general and work-related WPAI-AS subscores ($p<0.05$), and ESS score ($p<0.001$). Overall incidence of treatment-emergent adverse events was 14.4% for levocetirizine and 18.4% for placebo. The incidence of somnolence and fatigue was 0.7% and 1.8% with levocetirizine and 1% and 0% with placebo, respectively. The authors concluded that levocetirizine was well tolerated and was significantly more effective than placebo in improving the naso-ocular symptoms and health-related quality of life in U.S. patients with SAR.

Chronic Idiopathic Urticaria

cetirizine (Zyrtec) versus fexofenadine (Allegra)

An Indian study compared the efficacy and safety of cetirizine 10 mg and fexofenadine 180 mg in the treatment of CIU.¹³⁷ A total of 116 patients, aged 17 to 65 years, with CIU (urticarial wheals for at least two days per week for six consecutive weeks before entry) were enrolled in the randomized, double-blind, four-week long study. Ninety-seven patients (52 assigned to cetirizine, 45 assigned to fexofenadine) completed the study. The response in both the groups at the end of the treatment period was as follows: symptom free (cetirizine 51.9%, fexofenadine 4.4%); partial improvement (cetirizine 36.5%, fexofenadine 42.2%); no improvement (cetirizine 11.5%, fexofenadine 53.3%). Adverse effects noted were mild with no significant difference between the two.

desloratadine (Clarinet) versus levocetirizine (Xyzal)

In a multicenter, double-blind study, 886 patients with CIU were randomized to receive either levocetirizine 5 mg or desloratadine 5 mg once daily in the morning for four weeks.¹³⁸ Levocetirizine led to a significantly greater decrease in pruritus severity than desloratadine over the first treatment week ($p < 0.001$) and the entire four-week treatment period ($p = 0.004$). In addition, levocetirizine decreased pruritus duration and the mean CIU composite scores to a significantly greater extent than desloratadine during the first week ($p = 0.002$ and $p = 0.005$, respectively) and over the entire study ($p = 0.009$ and $p < 0.05$, respectively).

SUMMARY

All agents in the category have similar efficacy. Comparative data are available for cetirizine (Zyrtec), fexofenadine (Allegra), and loratadine (Claritin) with limited or no comparative data available for desloratadine (Clarinet) and levocetirizine (Xyzal). Some studies do indicate cetirizine may be more effective than loratadine at providing symptomatic relief; however, cetirizine causes significantly more sedation in many patients.

Although first generation antihistamines (e.g., diphenhydramine) are clinically effective, the rationale for using second generation antihistamines is that they control allergic rhinitis symptoms with less sedation and less anticholinergic effects. Cetirizine causes sedation in up to 14% of patients. Levocetirizine (Xyzal) is the active isomer of cetirizine. An increased risk of somnolence exists at higher doses of levocetirizine (Xyzal). Loratadine can be sedating at higher doses. Current data suggest the least likelihood of sedation with fexofenadine (Allegra) or desloratadine (Clarinet). Fexofenadine (Allegra) appears to cause the fewest CNS effects because its absorption into the brain is minimal. Cetirizine, loratadine, and fexofenadine are available over-the-counter (OTC) in various dosage forms.

Antihistamine/decongestant combination products should be administered when both the antihistaminic and nasal decongestant activity is desired.

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