



Antihistamines, Minimally Sedating Therapeutic Class Review (TCR)

February 8, 2019

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MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS^{1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17}

Drug	Rx/OTC	Manufacturer	Indication(s)
acrivastine/ pseudoephedrine (Semprex D [®])	Rx	Auxilium/Endo	<ul style="list-style-type: none"> Relief of symptoms associated with seasonal allergic rhinitis (AR) in adults and children ages ≥ 12 years
cetirizine tablets, oral liquid	Rx generic cetirizine solution OTC Zyrtec [®] tablet, Zyrtec [®] Allergy, Zyrtec [®] Children's Allergy	generic J&J 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 ages ≥ 2 years Relief of symptoms associated with seasonal AR due to allergens such as ragweed, grass, and tree pollens in adults and children ages ≥ 2 years Relief of symptoms associated with perennial AR due to allergens such as dust mites, animal dander, and molds in adults and children ages ≥ 6 months Treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in adults and children ages ≥ 6 months
cetirizine ODT (Zyrtec [®] Allergy ODT)	OTC	J&J Consumer	<ul style="list-style-type: none"> Temporary relief of symptoms of upper respiratory allergies (sneezing; runny nose; itchy, watery eyes; itchy throat or nose) in adults and children ages ≥ 6 months Relief of itching due to urticaria in patients in adults and children ages ≥ 6 months
cetirizine/ pseudoephedrine (Zyrtec-D [®] OTC 12 Hour)	OTC	generic J&J Consumer	<ul style="list-style-type: none"> Temporary relief of symptoms associated with sinusitis, allergic rhinitis, and other upper respiratory allergies (nasal congestion, sneezing; runny nose; itchy, watery eyes; itchy throat or nose) in adults and children ages ≥ 12 years
desloratadine (Clarinet [®] , Clarinet Redi-Tabs [®])	Rx	generic, Merck	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms of seasonal AR in patients ages ≥ 2 years Relief of nasal and non-nasal symptoms of perennial AR in patients ages ≥ 6 months Symptomatic relief of pruritus, reduction in the number of hives, and size of hives in patients with CIU ages ≥ 6 months
desloratadine ODT	Rx	generic	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms of seasonal AR in patients ages ≥ 2 years Relief of nasal and non-nasal symptoms of perennial AR in patients ages ≥ 6 months
desloratadine syrup (Clarinet [®])	Rx	Merck	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms of seasonal AR in patients ages ≥ 2 years Relief of nasal and non-nasal symptoms of perennial AR in patients ages ≥ 6 months Symptomatic relief of pruritus, reduction in the number of hives, and size of hives in patients with CIU ages ≥ 6 months
desloratadine/ pseudoephedrine (Clarinet-D [®] 12-Hour)	Rx	Merck	<ul style="list-style-type: none"> Relief of nasal and non-nasal symptoms of seasonal AR, including nasal congestion in adults and children ages ≥ 12 years

Rx = prescription required; OTC = over-the-counter; ODT = orally disintegrating tablet

FDA-Approved Indications (continued)

Drug	Rx/OTC	Manufacturer	Indication(s)
fexofenadine (Allegra®)	OTC	generic, Chattem Consumer	Relief of symptoms associated with hay fever or other upper respiratory allergies (sneezing; runny nose; itchy, watery eyes; itchy throat or nose) in adults and children ages ≥ 12 years
fexofenadine oral suspension	OTC	generic	
fexofenadine ODT (Allegra ODT®)	OTC	Chattem Consumer	Relief of symptoms associated with hay fever or other upper respiratory allergies (sneezing; runny nose; itchy, watery eyes; itchy throat or nose) in adults and children ages ≥ 6 years
fexofenadine/ pseudoephedrine (Allegra-D® 12 and 24 Hour)	OTC	generic, Chattem Consumer	Relief of symptoms associated with seasonal AR in adults and children ages ≥ 12 years
levocetirizine (Xyzal®)	Rx	generic	Relief of symptoms associated with perennial AR in adults and children ages 6 months to 2 years Treatment of uncomplicated skin manifestations of CIU in adults and children ages ≥ 6 months
levocetirizine (Xyzal® Allergy 24HR)	OTC	Chattem Consumer	Temporary relief of runny nose, sneezing, itchy/watery eyes, and itching of the nose or throat due to hay fever or other respiratory allergies in patients 6 to 64 years of age
levocetirizine syrup (Children’s Xyzal® Allergy 24HR; Xyzal Allergy 24HR))	OTC	Chattem Consumer	Temporary relief of runny nose, sneezing, itchy/watery eyes, and itching of the nose or throat due to hay fever or other respiratory allergies in patients ages ≥ 2 years
loratadine tablet, ODT, liquid capsule (Alavert® Quick Dissolving, Claritin®, Claritin Redi-Tabs, Claritin® Liqui-Gels)	OTC	generic, Pfizer Consumer, Bayer/Schering Plough	Temporary relief of symptoms due to hay fever or other respiratory allergies in adults and children ages ≥ 6 years
loratadine chewable tablet, ODT, syrup (Children’s Claritin®)	OTC	Bayer Healthcare/MSD Consumer	Temporary relief of symptoms due to hay fever or other respiratory allergies in patients ages ≥ 2 years Treatment of chronic idiopathic urticaria in patients ages ≥ 2 years
loratadine/pseudoephedrine (Alavert Allergy & Sinus, Claritin-D® 12 Hour, Claritin-D® 24 Hour)	OTC	generic, Pfizer Consumer, Bayer Healthcare/Schering Plough	Temporary relief of symptoms (sinus nasal congestion, runny nose, sneezing, itchy nose, watery eyes) due to common cold, hay fever, or other respiratory allergies or sinusitis in adults and children ages ≥ 12 years

Rx = prescription required; OTC = over-the-counter; ODT = orally disintegrating tablet

The combination loratadine/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, levocetirizine, loratadine, and fexofenadine are available over-the-counter (OTC) in various dosage forms.

The indication for seasonal allergic rhinitis (SAR) was removed from the labeling of the Xyzal approved for use by prescription only in February 2017. Xyzal Allergy 24HR was approved on January 31, 2017 for OTC use and is indicated for hay fever or other respiratory allergies.

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 2 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 1 or both forms of AR. 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 AR.^{20,21} Episodic AR is neither seasonal nor perennial, but is triggered by sporadic exposure to inhalant aeroallergens.

Estimates from 2008 suggest that 10% to 30% of adults and up to 40% of children experience AR.^{22,23} AR is the number 1 cause for work absenteeism. In children, approximately 2 million school days per year are lost due to AR.

Avoidance of allergens is fundamental to the management of AR. An effort to alter the home and work environments is crucial in the management of perennial allergies (e.g., dust and mold).²⁴ Patients with seasonal allergies (e.g., trees, weeds) experience difficulty avoiding common allergens during certain times each year. Initiation of treatment 1 to 2 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.^{25,26} Intranasal corticosteroids are most effective in controlling symptoms of AR, particularly in relieving nasal allergy symptoms (e.g., congestion, sneezing, runny nose). Alternative agents, such as leukotriene modifiers, cromolyn sodium, and antihistamine nasal sprays, may be appropriate in some patients.

Oral antihistamines are particularly effective for severe rhinorrhea, sneezing, pruritus, and conjunctivitis associated with AR, although less effective for nasal congestion.^{27,28} The usefulness of first-generation antihistamines is reduced because the agents may produce significant sedation, impair performance, and/or result in anticholinergic effects. Consequently, the second-generation (minimally sedating) antihistamines, associated with a lower incidence of side effects, are generally considered before first-generation (sedating) antihistamines, especially in older 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 the decongestant pseudoephedrine.

The 2008 updated guidelines from the AAAAI discuss developments in the management of AR.²⁹ Advantages and disadvantages of single and combination therapies of medications released in the last 10 years are discussed. Consideration of using a rhinitis action plan is advocated. Guidance for

assessing symptom severity and establishing a treatment plan is provided. 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 during pregnancy. The 2017 focused update to the AAAAI advises in patients who are 12 years or older, there is no clinical benefit of combination use of an oral antihistamine with an intranasal corticosteroid compared to using an intranasal corticosteroid alone.³⁰ Oral decongestants, including combination products in this review, are not recommended in children younger than 4 years of age.³¹

Additionally, clinical practice guidelines for management of AR published in February 2015 by the American Academy of Otolaryngology - Head and Neck Surgery, made some strong recommendations for clinicians treating patients.³² Intranasal steroids are strongly recommended for patients whose symptoms interfere with their quality of life and oral second generation/minimally-sedating antihistamines are strongly recommended for patients with primary complaints of sneezing and itching. The other recommendations included avoidance of known allergens and adding environmental controls when allergens have been identified and specific IgE (skin or blood) allergy testing for patients with a diagnosis of AR unresponsive to empiric treatment or when diagnosis is uncertain and the allergen is unknown. The panel also recommended against use of oral leukotriene receptor antagonists as first-line treatment for patients with AR.

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), when disease activity continues for more than 6 weeks, comprises 70% of all cases.³³ Chronic idiopathic urticaria can occur at any age; however, CIU is most common in young adults. In most patients, CIU 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 1 year, 50% have symptoms for longer than 5 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 histamine-1 (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 and if the patient is anxious and/or disturbed at night.³⁴ Approximately 50% of CIU cases will respond to antihistamine therapy.³⁵ If clinical response is not adequate, H₂-inhibitory drugs, such as cimetidine and ranitidine, may be added to the antihistamine.³⁶ Other agents reported to be beneficial in some cases include doxepin, a tricyclic antidepressant with anti-H₁ and anti-histamine-2 (H₂) properties, and the leukotriene receptor antagonist (off-label). In addition, the anti-immunoglobulin E (IgE) antibody omalizumab (Xolair[®]) is approved by the United States (US) Food and Drug Administration (FDA) to

treat CIU in patients aged 12 years and older who remain symptomatic despite H1 antihistamine therapy.³⁷ 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.³⁸

All minimally-sedating antihistamines are effective treatments for CIU.^{39,40,41,42} Little comparative data regarding the use of these agents for CIU are available; therefore, the focus of this review is AR.

PHARMACOLOGY^{43,44}

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

PHARMACOKINETICS^{45,46,47,48,49,50,51,52,53,54,55,56}

Drug (Metabolite)	T _{max} (hr)	T _{1/2} (hr)	Protein Binding (%)	Excretion (%)	Onset of Action (hr)	Duration of Action (hr)
acrivastine (Semprex-D) (1 metabolite)	1.14	1.9-3.5 (metabolite: 3.8)	50 ± 2	Urine: 84 Feces: 13	1-2	8
cetirizine (Zyrtec) (1 metabolite)	1	8.3	93	Urine: 50 Feces: 10	0.3-1	≥ 24
desloratadine (Clarinet) (6 metabolites)	3	27	82-87	Urine: 43.5 Feces: 43.5	1	24
fexofenadine (Allegra) (no metabolites)	2.6	14.4	60-70	Urine: 11 Feces: 80	1	> 12
fexofenadine ODT (Allegra ODT) (no metabolites)	2	14.4	60-70	Urine: 11 Feces: 80	1	> 12
levocetirizine (Xyzal) (4 metabolites)	0.9	8-9	91-92	Urine: 85 Feces: 13	1	24
loratadine (12 metabolites, including desloratadine)	1.3 (2.5)	8.4-18.2 (metabolites: 17.5-28)	98 (73-76)	Trace	1-3	24

Results are mean ± standard deviation.

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

CONTRAINDICATIONS/WARNINGS^{57,58,59,60,61,62,63}

Pseudoephedrine, the decongestant component of Allegra-D, Claritin-D, Clarinet-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 2 weeks) discontinued a MAO inhibitor. In addition to these contraindications, pseudoephedrine should be carefully monitored in patients with hypertension, diabetes mellitus, ischemic heart disease, increased intraocular pressure, hyperthyroidism, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, or renal impairment. Pseudoephedrine has also been associated with adverse effects, such as insomnia, tremor, and arrhythmias. Furthermore, pseudoephedrine has been associated with central nervous system (CNS) over-stimulation associated with convulsions, and may eventually lead to hypotension with

cardiovascular collapse. Hypersensitivity reactions including rash, pruritus, urticaria, edema, dyspnea, and anaphylaxis have been reported with desloratadine. Additionally, there are post-marketing reports of tachycardia and movement disorders (extrapyramidal symptoms, dystonia) with use of desloratadine (Clarinet) as a single agent and in combination with pseudoephedrine (Clarinet-D).^{64,65} It should also be noted that levocetirizine (Xyzal) is contraindicated in children ages 6 months to 11 years of age with renal impairment and in patients with end stage renal disease with a creatinine clearance (CrCl) < 10 mL/min or undergoing hemodialysis.⁶⁶ 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 patients with a known hypersensitivity to any component of the product or to hydroxyzine.

DRUG INTERACTIONS^{67,68,69,70,71,72,73,74,75,76}

Drug	azithromycin	erythromycin	Grapefruit Juice*	ketoconazole	theophylline	Al and Mg Containing Antacids
acrivastine (Semprex D)	--	--	--	--	--	--
cetirizine (Zyrtec)	--	--	--	--	16% decrease in cetirizine clearance	--
desloratadine (Clarinet)	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)	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)	--	--	--	--	--	--
loratadine (Claritin)	--	increase in loratadine levels	--	increase in loratadine levels	--	--

Al = aluminum; Mg = magnesium; C_{max} = maximum serum concentration

*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.

No formal drug interaction studies for acrivastine/pseudoephedrine (Semprex-D) have been performed.

In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes; however, no *in vivo* drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine.

Pseudoephedrine, contained in the combination products in this review (Allegra-D, Clarinex-D, Claritin-D, Semprex-D, Zyrtec-D), may reduce the antihypertensive effects of some medications, including beta-adrenergic blockers. Increased ectopic pacemaker activity can occur when pseudoephedrine is used concomitantly with digoxin. Pseudoephedrine may potentiate the effects of MAO inhibitors; therefore, it should not be taken within 14 days of an MAO inhibitor. Concomitant administration of pseudoephedrine with alcohol and other CNS depressants may result in additional reductions in alertness and impairment of CNS performance and should be avoided.

Coadministration of desloratadine with cimetidine or fluoxetine results in increased plasma concentrations of desloratadine and its metabolite.

ADVERSE EFFECTS

Adults^{77,78,79,80,81,82,83,84,85,86,87,88,89}

Drug	Dry Mouth	Dyspepsia	Fatigue	Headache	Insomnia	Nausea	Somnolence
acrivastine/pseudoephedrine (Semprex D)	7	2	nr	19	4	2	12
Cetirizine (Zyrtec)	5	< 2	5.9	> 2	< 2	> 2	11-14
cetirizine/pseudoephedrine (Zyrtec D)	3.6	reported	2.4	reported	4	reported	1.9
Desloratadine (Clarinex)	3	3	2.1-5	14	nr	5	2.1-9.1
desloratadine/pseudoephedrine (Clarinex-D 12-Hour)	8	nr	4	8	10	2	3
desloratadine/ pseudoephedrine (Clarinex-D 24-Hour)	8	nr	3	6	5	2	3
fexofenadine (Allegra)	nr	1.3	1.3	10.6	< 1	1.6	1.3-2.2
fexofenadine/pseudoephedrine (Allegra-D 12-hour)	2.8	2.8	nr	13	12.6	7.4	nr
levocetirizine (Xyzal)	2-3	nr	1-4	nr	nr	nr	5-6
loratadine (Claritin)	2-4	2-3	4-6	12	1-4	2	8
loratadine/pseudoephedrine 12 hr (Claritin D-12 hr)	14	3	4	19	16	3	7
loratadine/pseudoephedrine 24 hr (Claritin D-24 hr)	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^{90,91,92,93,94}

Drug	Abdominal Pain	Cough	Fatigue	Nausea	Pharyngitis	Somnolence	Headache
cetirizine (Zyrtec)	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)	nr	10.8	5	3-5	3-4.5	9.1	14
fexofenadine (Allegra)	nr	3.8	nr	nr	nr	nr	7.2
levocetirizine (Xyzal)	nr	3	nr	nr	nr	3	nr
loratadine (Claritin)	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.

A multicenter, double-blind, randomized, placebo-controlled, parallel-group, 2-week trial was conducted in 453 preschool children ages 2 to 5 years old with AR to compare the safety and tolerability of twice daily fexofenadine (Allegra) 30 mg versus placebo.⁹⁵ 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 2 to 5 years of age with allergic rhinitis.

A meta-analysis including 16 double-blind, placebo-controlled studies concluded that first generation antihistamines (diphenhydramine, triprolidine, terfenadine, d-chlorpheniramine, clemastine) significantly impair driving performance after both 1-time and repeated (daily) administration.⁹⁶ Second generation antihistamines (cetirizine, loratadine, and acrivastine) may also impair driving performance, but to a lesser magnitude. The third generation antihistamine (fexofenadine) produced no driving impairment after both 1-time and repeated administration. In addition, a randomized, double-blind, cross-over study brake reaction time was significantly faster with desloratadine than diphenhydramine) or placebo.⁹⁷

Post-marketing studies reported low risk of sedation with loratadine, cetirizine, fexofenadine, and acrivastine, but reported a lower risk with loratadine and fexofenadine.⁹⁸

A randomized, double-blind study compared the somnolence and motivation profiles of loratadine and cetirizine in 60 patients aged 12 years and older and actively exhibiting symptoms of AR.⁹⁹ Based on electronic patient diaries using a visual analog scale at 4 times during the workday, a significantly greater degree of somnolence and lower level of motivation were reported with cetirizine 10 mg compared to loratadine 10 mg.

Cases of severe skin reactions, including acute generalized exanthematous pustulosis (AGEP), have been reported postmarketing with use of products that contain pseudoephedrine.

There have been reports of seizures in patients with and without a known seizure disorder and febrile seizures associated with levocetirizine use.

SPECIAL POPULATIONS^{100,101,102,103,104,105,106,107,108,109,110,111,112}

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 6 months of age have not been established. The recommended doses for children ages 6 months to 11 years should not be exceeded. Use of the OTC levocetirizine syrup (Children's Xyzal Allergy 24HR) is not approved for use in children younger than 2 years.

Safety and effectiveness of fexofenadine (Allegra) in pediatric patients have been established in ages 2 years and older for the liquid formulation. Physician oversight of fexofenadine therapy is recommended for patients 6 months to 23 months of age. Fexofenadine ODT (Children's Allegra) is approved for use in children 6 years and older, and fexofenadine oral tablets are approved in ages 12 years and older.

Safety and effectiveness of desloratadine (Clarinex) and cetirizine (Zyrtec) in pediatric patients under 6 months of age have not been established.

Safety and effectiveness of loratadine (Claritin) in pediatric patients under 2 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), desloratadine/pseudoephedrine (Clarinex-D), cetirizine/pseudoephedrine (Zyrtec-D), and fexofenadine/fexofenadine ODT (Allegra, Allegra ODT) are Pregnancy Category C.

Hepatic Impairment

A reduction in dosage or dosage frequency is recommended for cetirizine (Zyrtec) in patients with hepatic impairment. Use of cetirizine in children less than 6 years of age with impaired 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 reduction in dosage or dosage frequency is recommended for cetirizine (Zyrtec) with renal impairment. Use of cetirizine in children less than 6 years of age with impaired renal function is not recommended.

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.

Elderly

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

Labeling for cetirizine, fexofenadine, and levocetirizine OTC products advise to consult a physician for use in patients 65 years and older.

Antihistamines are more likely to cause dizziness, sedation, bladder-neck obstruction, and hypotension in elderly patients. The elderly are also more likely to have adverse reactions to pseudoephedrine.

DOSAGES^{113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128}

Drug	Adult Dose (Including Children 12 Years and Older)	Pediatric Dose (Less Than 12 Years Old)	Availability	Rx/OTC
acrivastine/pseudoephedrine (Semprex-D)	1 capsule 4 times daily	--	8 mg/60 mg capsules	Rx
cetirizine (Zyrtec, Zyrtec ODT)	5 or 10 mg daily 65 years and older: 5 mg daily	6 – 11 years: 5 or 10 mg daily 2 – 5 years: 2.5 – 5 mg (½ – 1 tsp or 5 mg chewable tab) daily 12 – 23 months: may increase to 2.5 mg (½ tsp) every 12 hours 6 – 11 months: 2.5 mg (½ tsp) daily	1 mg/mL solution	Rx
			5 mg (generic only) and 10 mg tablets 5 mg and 10 mg chewable tablets (generic only) 1 mg/mL syrup 10 mg ODT (brand only) 10 mg liquid filled capsules	OTC
cetirizine/pseudoephedrine (Zyrtec-D 12 Hour)	1 tablet twice daily	--	5 mg/120 mg ER (12 hour) tablets	OTC
desloratadine (Clarinet)	5 mg daily	6 – 11 years: 2.5 mg (1 tsp) daily 12 months – 5 years: 1.25 mg (½ tsp) daily 6 – 11 months: 1 mg (2 mL) daily	5 mg tablets 0.5 mg/mL syrup (brand only) 2.5 mg and 5 mg ODT (generic only)	Rx
desloratadine/pseudoephedrine (Clarinet-D 12-Hour)	1 tablet every 12 hours	--	2.5 mg/120 mg ER (12 hour) tablets	Rx
fexofenadine (Allegra)	60 mg twice daily or 180 mg daily		60 mg and 180 mg tablets 180 mg liquid filled capsule (brand only)	OTC
fexofenadine oral suspension (Allegra Oral Suspension)*	60 mg (2 tsp) twice daily	2 – 11 years: 30 mg (1 tsp) twice daily	6 mg/mL oral suspension	OTC
fexofenadine ODT (Allegra ODT)	60 mg twice daily	6 – 11 years: 30 mg twice daily on an empty stomach	30 mg orally disintegrating tablet (brand only)	OTC

ER = extended-release; Rx = prescription required; OTC = over-the-counter; ODT = orally disintegrating tablet

Dosages (continued)

Drug	Adult Dose (Including Children 12 Years and Older)	Pediatric Dose (Less Than 12 Years Old)	Availability	Rx/OTC
fexofenadine/pseudoephedrine 12-hour (Allegra-D 12 hour)	1 tablet twice daily	--	60 mg /120 mg ER (12 hour) tablets	OTC
fexofenadine/pseudoephedrine 24-hour (Allegra-D 24 hour)	1 tablet once daily on an empty stomach (ages 12 years and older)	--	180 mg /240 mg ER (24 hour) tablets	OTC
levocetirizine (Xyzal [Rx], Xyzal Allergy 24HR [OTC]) [†]	5 mg once daily in the evening OTC – 2.5 mg (1/2 tablet) may be appropriate for less severe symptoms	6 – 11 years: (Rx and OTC - respiratory allergies) 2.5 mg (1/2 tablets or 1 tsp) once daily in the evening	5 mg tablets (generic only) 0.5 mg/mL oral solution (generic only)	Rx
		Chronic idiopathic urticaria 6 months – 5 years (Rx only): 1.25 mg (½ tsp) once daily in the evening Perennial allergic rhinitis 6 months – 2 years (Rx only) 1.25 mg (½ tsp) once daily in the evening	5 mg tablets 0.5 mg/mL oral solution (brand only)	OTC
loratadine (Alavert [ODT only], Claritin)	10 mg daily	6 – 11 years: 10 mg once daily 2 – 5 years: 5 mg (1 tsp) once daily	10 mg tablets 5mg (Claritin brand only) and 10 mg ODT 1 mg/mL syrup (for children) 10 mg liquid filled capsules	OTC
loratadine chewable tablet (Children’s Claritin)	10 mg (2 chew tablets) daily	6 – 11 years: 10 mg (2 chew tablets) daily 2 – 5 years: 5 mg (1 chew tablet) daily	5 mg chewable tablets	OTC

ER = extended-release; Rx = prescription required; OTC = over-the-counter; ODT = orally disintegrating tablet

Dosages (continued)

Drug	Adult Dose (Including Children 12 Years and Older)	Pediatric Dose (Less Than 12 Years Old)	Availability	Rx/OTC
loratadine/pseudoephedrine 12-hour (Alavert-D 12-hour Allergy & Sinus; Claritin-D 12-Hour)	1 tablet twice daily	--	5 mg/120 mg ER (12 hour) tablets	OTC
loratadine/pseudoephedrine 24-hour (Claritin-D 24-Hour)	1 tablet daily	--	10 mg/240 mg ER (24 hour) tablets	OTC

ER = extended-release; Rx = prescription required; OTC = over-the-counter; ODT = orally disintegrating tablet

* 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 CIU, in children 6 months to less than 6 years of age, it requires evaluation by a physician and a prescription.¹²⁹ Dosing recommendation is based on previously recommended prescription suspension data (6 months to younger than 2 years of age: 15 mg [2.5 mL of oral suspension] twice daily).

Cetirizine, levocetirizine, 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.

† Xyzal Allergy 24HR (levocetirizine OTC) is not indicated in children < 6 years of age. A doctor should be consulted for use in those 65 years and older.

In adults with hepatic impairment, a starting desloratadine (Clarinet) dose of 5 mg every other day is recommended. Use of desloratadine/pseudoephedrine (Clarinet-D) should generally be avoided in patients with hepatic impairment.

In adults and children 6 years of age and over with liver failure, the starting dose of loratadine (Claritin) should be 10 mg every other day. In children 2 to 5 years of age with liver failure, the starting dose should be 5 mg every other day.

A fexofenadine/fexofenadine ODT (Allegra, Allegra ODT) dose of 60 mg once daily is recommended as the starting dose in adults with decreased renal function. For pediatric patients with decreased renal function, the recommended starting dose of fexofenadine (Allegra) is 30 mg once daily for patients 2 to 11 years of age, and 15 mg once daily for patients 6 months to less than 2 years of age.

In adults with renal impairment, a starting desloratadine (Clarinet) dose of 5 mg every other day is recommended. Use of desloratadine/pseudoephedrine (Clarinet-D) should generally be avoided in patients with renal impairment.

In adults and children 6 years of age and over with renal insufficiency (GFR < 30 mL/min), the starting dose of loratadine (Claritin) should be 10 mg every other day. In children 2 to 5 years of age with renal insufficiency, the starting dose should be 5 mg every other day.

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)

In a comparative study, 575 allergic patients were exposed to ragweed pollen in an environmental exposure unit for 2 days and randomized in a double-blind fashion to once-daily cetirizine 10 mg, fexofenadine 180 mg, or placebo.¹³⁰ 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 3 periods: period 1 (TSSC 0 to 5 hours after the first dose), period 2 (TSSC 21 to 24 hours after the first dose), and period 3 (TSSC 0 to 2 hours after the second dose). The onset of action was comparable, and similar efficacy was observed in period 1 for both active treatments. For period 2, 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 3, 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 5 to 12 hours after pollen exposure in an environmental exposure unit.¹³¹ 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 3 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 2 weeks for the treatment of seasonal allergic rhinitis (SAR).¹³² The total symptom score (TSS) was calculated for 4 individual symptoms: sneezing, rhinorrhea, itchy nose, palate or throat, and itchy, watery, or red eyes. There were no differences in efficacy between the 2 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 2-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.¹³³ Improvement in daily 12-hour reflective and instantaneous individual symptoms and total symptom score (TSS) were statistically equivalent between the 2 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.¹³⁴ Subjects were randomized to 2 days at the environmental exposure unit (6 to 7 hours daily) along with administration of 1 of the 2 active treatments or placebo. Evaluation of symptom scores indicated onset of action was earlier with cetirizine 10 mg (1 hour, $p\leq 0.001$) than with loratadine 10 mg (3 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.¹³⁵ Ninety patients with moderate to severe AR were given cetirizine 10 mg, loratadine 10 mg, or placebo daily for 4 weeks. The investigators demonstrated that the 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 (2 to 6 years of age) with PAR were randomized to receive cetirizine or loratadine 0.2 mg/kg once daily for 28 days.¹³⁶ 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 (Clarinex) 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 2 weeks of treatment with fexofenadine 180 mg or desloratadine 5 mg taken once daily in the morning.¹³⁷ 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, 2-phase, multicenter study was conducted to compare therapeutic responses to loratadine and fexofenadine in patients who failed initial therapy with the other drug.¹³⁸ In the study, 661 patients were randomized to receive loratadine 10 mg once daily or fexofenadine 60 mg twice daily for 14 days (phase 1); non-responders subsequently received the alternate medication for 14 days (phase 2). Mean decreases in TSS were significantly greater with loratadine than with fexofenadine for the patients who completed phase 1 (-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.¹³⁹ In the study, 688 patients were randomized to receive fexofenadine 120 mg, loratadine 10 mg, or placebo daily for 2 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.¹⁴⁰ Patients were randomized to loratadine 10 mg once daily, fexofenadine 60 mg twice daily, or matching placebo for 7 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

Levocetirizine demonstrated efficacy versus placebo in 6 placebo-controlled, randomized, double-blind controlled trials in patients with seasonal and perennial allergic rhinitis, including patients ages of 12 to 17 years.¹⁴¹ Total symptom scores were significantly reduced in the active treatment groups in both seasonal and perennial AR trials ($p<0.001$).

Chronic Idiopathic Urticaria

cetirizine (Zyrtec) versus placebo

Cetirizine demonstrated efficacy versus placebo in two 4-week randomized, double-blind, placebo-controlled trials in patients with CIU.¹⁴² In general, the 10 mg dose was more effective than the 5 mg dose; 20 mg (not FDA-approved) did not offer any additional benefit over 10 mg.

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 4 weeks.¹⁴³ Levocetirizine led to a significantly greater decrease in pruritus severity than desloratadine over the first treatment week ($p < 0.001$) and the entire 4-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, levocetirizine, 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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