

Pharmacy & Therapeutics Committees
Non-Sedating/Low Sedating Antihistamines
9/2000

Recommendations:

Loratadine (Claritin®) and Claritin D 12 hour (5 mg with 120 of pseudoephedrine) are the P&T recommended formulary non-sedating antihistamines with automatic substitution for fexofenadine (Allegra®/Allegra D®), cetirizine (Zyrtec®), and Semprex D (8 mg acrivastine with 60 mg pseudoephedrine). They will be stocked in the following dosage forms: Claritin 10 mg, Claritin D 12 hour, and as the syrup 1 mg/ml for pediatric patients.

P&T/MEC APPROVED 11/2000

Non Formulary Medication Ordered	P&T/MEC Approved AutoSubstitution
Allegra 30 mg every day, 6-11 years old with renal dysfunction	Claritin 10 mg every other day
Allegra 30 mg BID, 6-11 years old	Claritin 10 mg every day
Allegra 60 mg every day, 12 years and older with renal dysfunction	Claritin 10 mg every other day
Allegra 60 mg BID, 12 years and older	Claritin 10 mg every day
Allegra 180 mg every day, 12 years and older	Claritin 10 mg every day
Allegra D one every 12 hours, 12 years and older	Claritin D one every 12 hours
Clarinx 5 mg every other day, 12 years and older: Clcr < 30 ml/min or liver impairment	Claritin 10 mg every other day
Clarinx 5 mg every day, 12 years and older	Claritin 10 mg every day
Zyrtec 2.5 mg every day, 6 months to < 2 years Maximum dose: 2.5 mg every 12 hours	Do not substitute
Zyrtec 2.5 mg every day, 2-5 years old Maximum 2.5 mg every 12 hours or 5 mg once daily	Claritin 5 mg every day
Zyrtec 5 mg every day, 6-11 years old: clcr < 31 ml/min, on hemodialysis or hepatically impaired	Claritin 10 mg every other day
Zyrtec 5-10 mg every day, 6-11 years old	Claritin 10 mg every day
Zyrtec 5 mg every day, 12 years and older: clcr < 31 ml/min, on hemodialysis or hepatically impaired	Claritin 10 mg every other day
Zyrtec 5-10 mg every day, 12 years and older	Claritin 10 mg every day

*Note Claritin dosage in patients 6 years and older with hepatic failure or clcr < 30 ml/min is 10 mg every other day.

Findings:

- The second-generation antihistamines demonstrate comparable efficacy, the choice of one second-generation antihistamine over another for the treatment of seasonal or perennial allergic rhinitis and/or urticaria should be based on availability, administration interval, dosage form, multiple indications, contraindications, adverse effects, and cost.
- Indications for the agents are similar (seasonal allergic rhinitis, perennial allergic rhinitis, and chronic urticaria)
- To date, comparative studies of second-generation antihistamines have not produced any compelling evidence that one agent is superior to the others. The main disadvantages that may impact compliance, are the approved three-times-daily dosing of acrivastine (Semprex D: acrivastine 8 mg/pseudoephedrine 60 mg) and the twice-daily dosing of fexofenadine. It has been noted that most comparative studies do not document reliable pollen count or ongoing exposure to allergens. Also, many of the studies were limited by small sample size, varying study durations (single-dose to 8 weeks), and use of different evaluation methods.
- Cetirizine, fexofenadine, and loratadine have shown efficacy in treating urticarial conditions compared to placebo. Insufficient data has been published to demonstrate superiority of any available second-generation antihistamine for the treatment of chronic urticaria.
- All three agents (loratadine (Claritin®), fexofenadine (Allegra®), cetirizine(Zyrtec®) are FDA approved for patients ≥ 6 years old.
- Loratadine (Claritin®) and cetirizine (Zyrtec®) are available in tablets and syrup. Cetirizine's banana-grape flavored syrup is distasteful according to some pediatric patients.
- Loratadine (Claritin®) is the most commonly used product accounting for 63% of current usage in Richmond.
- None of agents when combined with pseudoephedrine are FDA approved for use in children < 12 years of age.

- Fexofenadine (Allegra®), active metabolite of terfenadine, is usually administered twice daily versus once daily for the other agents.
- The non-sedating/low sedating antihistamines have a slower onset of action and prolonged duration of effect when compared to the first generation agents.
- These agents are highly selective peripheral histamine H₁-receptor antagonists with little or no central, anticholinergic, or autonomic nervous system effects. These agents distribute poorly or not appreciably into the CNS at usual dosages.
- Cetirizine, the active metabolite of hydroxyzine, causes more sedation as is classified as a low sedating antihistamine and effects may be additive with other CNS depressants.
- First-generation antihistamines (i.e., chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine) are not selective, binding to central and peripheral H₁-receptors, while the second-generation antihistamines (i.e., cetirizine, fexofenadine, loratadine) bind preferentially to peripheral H₁-receptors. Most first-generation antihistamines are lipid soluble and cross the blood-brain-barrier easily, resulting in numerous adverse central nervous system effects, including motor impairment. The level of anti-cholinergic activity among first-generation antihistamines is also very high. It may be beneficial to use a more sedating first-generation antihistamine at night, particularly in patients who may have insomnia.
- The second-generation agents are large, lipophilic, highly protein-bound, and do not easily pass through the blood-brain barrier. Although the incidence of sedative effects may seem high for the agents to be considered low- or non-sedating, it is less than the incidence seen with the first-generation agents (chlorpheniramine 45%, diphenhydramine 50% and hydroxyzine 80%). The sedation caused by cetirizine is most likely dose-related. In one comparative dose study, 5-mg doses demonstrated a significantly lower incidence of sedation than the 10-mg and 20-mg doses (11% v 15% v 21%, respectively). In 1993, the Pulmonary-Allergy Drugs Committee of the FDA concluded that cetirizine's sedative effects were comparable to those of the first-generation antihistamines, leading to warnings about somnolence and danger with driving and operating heavy machinery in the package insert. Cetirizine is thus considered to be a low-sedating second-generation antihistamine.
- Loratadine serum concentrations are highly affected by the cytochrome P-450 system, unlike cetirizine and fexofenadine. Cetirizine, fexofenadine, and loratadine are not dialyzable.
- Of the currently available agents, loratadine's plasma levels have been increased by coadministration with azole antifungals, cimetidine, and macrolide antibiotics.^{16,130} Although plasma levels increased, there were no electrocardiographic changes or other adverse effects noted when these agents were co-administered in healthy volunteers.
- Cetirizine is excreted mainly unchanged in the urine and is not removed by hemodialysis.

Table 2. Indications *

Indication	Cetirizine	Fexofenadine	Loratadine
Seasonal Allergic Rhinitis	YES	YES	YES
Perennial Allergic Rhinitis	YES	INV	INV
Chronic Urticaria	YES	NDA in 7/98	YES

* FDA = FDA-approved indication. INV= investigational use. NDA = New Drug Application submitted.

Table 3. Pharmacokinetic/Pharmacodynamic Parameters for Oral Dosage Forms^{1,2,3,16,17,24,27,28*}

Parameter	Acrivastine	Cetirizine (Zytrec)	Fexofenadine (Allegra)	Loratadine (Claritin)
Onset of effect (hours)	0.5	1	Adults : 1 Children: 1 - 2	1 to 3
t _{max} (hours) †	1.14+/- 0.23	1	2.6	1.3 - 2.5
Duration of effect (hours)	6	≤ 24	Rhinitis: ≥ 12 Children wheal / flare: 1 - 24 dose-dependent	≤ 24
Effect of Food	AUC no effect	T _{max} delayed 1.7 hrs; C _{max} decreased 23%; AUC no effect	High-fat meal: C _{max} decreased 25%; AUC decreased 24%	t _{max} delayed one hour; C _{max} not affected; AUC increased 40%
Plasma Protein Binding	50 - 52%	93%	60 - 70%	97 - 99% (75%=metabolite)
Volume of distribution (L/kg)‡	Adults: 0.46 - 0.82	Adults: 0.41 Children: 0.7	5.4 - 5.8	119
Route of Metabolism §	Hepatic cyt P-450	Low hepatic cyt P-450 metabolism (oxidative dealkylation)	Very low cyt P-450 metabolism (0.5 - 1.5%)	High hepatic cyt P-450 metabolism via 3A4 + 2D6 isoenzymes
Active Metabolites	Propionic acid (PA)	None	None	Desloratadine (DL)
Route of elimination	84% urine 67% unchanged 15-17% metabolized 13% feces	70% urine (40% in kids) 50% unchanged 10% feces	12% urine 95% unchanged 80% feces	40% urine 42% feces
t _{1/2} ¶ Parent compound (metabolite) (hrs)	At steady state: 3.5 +/- 1.9 (PA: 3.8 +/- 1.4)	Adults: 7.4 - 9 Children 4 -12 yo: 5.5 -7 Children < 4 yo: 4.9 Infants ≤ 12 months: 0.8 - 6.5 Geriatric/liver disease: 11 - 13.5 Renal failure: 19 - 21	Adults: 14 - 18 Children: 17.6 - 18.3 Geriatrics: Same as adult Renal failure: CrCl 41 - 80 mL/min: 22 - 29 CrCl 11 - 40 mL/min: 24 - 31 Dialysis: 18 - 24	Adults: 8.4, (DL: 28) Children 6-12: same as adult Geriatrics: 6.7 - 37, (DL:11 - 38) Liver disease: 24, (DL: 27) Renal failure (CrCl < 30 mL/min):7.6, (DL: 23.9)

* Data is the same for adults and children, unless noted in table. † t_{max} = time to reach maximum serum concentration. ‡ L = liter, kg = kilogram; acrivastine range reflects single-dose to steady-state. § cyt P-450 = cytochrome P-450 enzyme system. || PA = Propionic acid; DL = Desloratadine. ¶ t_{1/2} = half-life; hrs = hours; yo = years old; CrCl = creatinine clearance; mL = milliliters; min = minute.

	Cetirizine(Zytrec)	Loratadine(Claritin)	Fexofenadine (Allegra)
Allergic Rhinitis/Urticaria	+	+	+
Seasonal Allergic Rhinitis			+
Chronic Idiopathic Urticaria			+

- In the treatment of seasonal allergic rhinitis they are more likely to be beneficial when started before pollen counts increase and if administered daily during the pollen season.
- Seasonal allergic rhinitis is caused by reactions to molds and pollens and differs with geographic regions. It is predominantly caused by outdoor aeroallergens. Perennial allergic rhinitis (PAR) is caused by constant exposure to indoor environmental allergens such as dust mites and animal or occupational allergens, as well as molds and pollen that exist throughout the year.¹⁰
- The Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology acknowledged that antihistamines may be effective when used on demand, but recommended administration either prophylactically (2-5 hours before allergen exposure) or on a regular basis when needed chronically. They noted that antihistamines work best when taken continuously.¹⁰
- In two loratadine studies, the investigators conducted a cross-over to the other treatment arm for non-responders.^{33,62} In the first study conducted in patients with PAR, all non-responders to terfenadine responded to loratadine. Only four of the nine patients who initially did not respond to loratadine, received benefit from switching to terfenadine.³³ In the second study conducted in patients with SAR, 35.5% of initial non-responders to fexofenadine experienced improvement when switched to loratadine, while 24.8% of non-responders to loratadine benefited from a therapeutic switch to fexofenadine.⁶²
- According to the Institute for Safe Medication Practices (ISMP) there is a potential for medication errors due to the similarity between the brand name of cetirizine, Zyrtec[®], and the antipsychotic olanzapine (Zyprexa[®]). To date over 30 case reports have been submitted during post-marketing surveillance to the FDA's Medwatch and the United States Pharmacopoeia (USP)-ISMP medication error databases. Besides the similarity in names, the products are taken once daily, have similar daily dosing (5-10 mg), are available in similar strengths (5 mg and 10 mg) and similar tablets (white, film-coated). Potential sources of error include misreading poorly written prescriptions and removing the wrong drug from the shelf since the drugs are often stored next to each other.¹⁰⁹
- Patients taking the extended-release loratadine combination product Claritin-D[®] 24 hour must additionally be advised to take the product with a full glass of water, without chewing or breaking the tablet.¹³⁵ In 1997, five cases of gastrointestinal obstruction with Claritin-D[®] 24 hour were reported. In some cases, the tablet had adhered to the mucosal surface, making it impossible to dislodge without esophagoscopy under general anesthesia.⁵² In December 1998, Claritin-D[®] 24 hour was changed from a large, round tablet to an oval tablet, with a polished coating of sugar and wax to facilitate swallowing. Patients with a history of swallowing abnormalities or difficulty swallowing should not take the old formulation or the new oval Claritin-D[®] 24 hour.¹³⁶

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Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis.

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BACKGROUND: In vitro studies have shown much higher H1-receptor antagonist potency with desloratadine (DL) compared to fexofenadine (FEX), although it is unclear whether this has any clinical relevance on disease control parameters in seasonal allergic rhinitis (SAR), especially for nasal congestion. **OBJECTIVE:** To compare the relative efficacy between presently recommended doses of DL and FEX on daily measurements of peak nasal inspiratory flow (PNIF) and nasal symptoms in SAR. **METHODS:** 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 once daily treatment with (a) 180 mg FEX or (b) 5 mg DL, taken in the morning. There was a 7-10 day placebo run-in and washout prior to each randomized treatment. Measurements were made in the morning (AM) and in the evening (PM) for PNIF (the primary outcome variable), nasal and eye symptoms. The average of AM/PM values were used for analysis. **RESULTS:** There were significant ($P < 0.05$) improvements, compared to placebo, with FEX and DL, 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. Values for PNIF (L/min) for mean placebo baseline, mean difference from baseline (95% CI for difference) were 126, 10 (4-16) for FEX; and 122, 11 (4-17) for DL. The mean difference (95% CI) between FEX vs. DL was 1 L/min (-7-8). Values for total nasal symptoms (out of 12) were: 3.2, 0.7 (0.2-1.2) for FEX; and 3.4, 0.9 (0.3-1.5) for DL, and for nasal blockage (out of 3) were: 1.1, 0.2 (0.1-0.4) for FEX; and 1.2, 0.3 (0.1-0.5) for DL. The mean difference (95% CI) in total nasal symptoms and nasal blockage between FEX vs. DL was 0.1 (-0.6-0.8) and 0.1 (-0.2-0.3), respectively. **CONCLUSIONS:** Recommended once daily doses of fexofenadine and desloratadine were equally effective in improving nasal peak flow and nasal symptoms in SAR.

Clin Ther. 2000 Jun;22(6):760-9.

Efficacy and tolerability of loratadine versus fexofenadine in the treatment of seasonal allergic rhinitis: a double-blind comparison with crossover treatment of nonresponders.

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BACKGROUND: Nonsedating antihistamines are well-established treatment for seasonal allergic rhinitis (SAR), but patients do not always respond to the first antihistamine prescribed. **OBJECTIVE:** This double-blind, double-dummy, randomized, 2-phase, multicenter study was designed primarily to compare the therapeutic responses to loratadine and fexofenadine in patients who failed initial therapy with the other drug. **METHODS:** Male and female patients aged 12 to 60 years received loratadine 10 mg once daily ($n = 331$) or fexofenadine 60 mg twice daily ($n = 328$) for 14 days (phase 1); nonresponders (ie, those who had $<25\%$ reduction in the sum of 5 SAR symptoms rated by the investigator on a 4-point scale) subsequently received the alternate medication for 14 days (phase 2). The investigator's rating of relief (complete, marked, moderate, or slight relief of symptoms or treatment failure) at the end of phase 2 was the primary efficacy measure; changes in total symptom severity (TSS) assessed by the investigator (4-point scale) and the patient (11-point visual analog scale) were secondary measures. **RESULTS:** Mean decreases in TSS were significantly greater with loratadine than with fexofenadine for the 659 patients who completed phase 1 (-12.7 vs -10.2, respectively; $P = 0.019$; patient assessment) and for the 389 patients who responded to initial therapy (-6.6 vs -6.1, respectively; $P = 0.037$; investigator assessment). Of the 389 patients who responded to initial therapy, 61.0% had received loratadine and 57.0% had received fexofenadine. More nonresponders to initial therapy had moderate, marked, or complete relief of symptoms after switching to loratadine than after switching to fexofenadine (62.4% vs 51.2%, respectively; $P = 0.005$) and treatment failure in 10.6% vs 21.7%, respectively ($P = 0.011$). **CONCLUSION:** Overall, loratadine provided significantly better therapeutic response than fexofenadine in patients who failed to respond to initial therapy with the other drug.

J Allergy Clin Immunol. 1999 Nov;104(5):927-33.

Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis.

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BACKGROUND: Fexofenadine hydrochloride (HCl) is a new H₁ antihistamine used twice daily in some countries. **OBJECTIVE:** A multicenter, double-blind, parallel-group, placebo-controlled trial compared the efficacy and safety of fexofenadine HCl (120 and 180 mg administered once daily) and cetirizine (10 mg once daily) in the treatment of seasonal allergic rhinitis. **METHODS:** After a 3- to 5-day run-in period, patients meeting entrance criteria were randomized to receive placebo, fexofenadine HCl 120 mg once daily, fexofenadine HCl 180 mg once daily, or cetirizine 10 mg once daily (active control) for 2 weeks. Eight hundred twenty-one patients comprised the intention-to-treat population and 722 patients completed the study. Symptom assessments were conducted 12 hours after the dose for the previous 12 hours and again at 24 hours after the dose for the previous 12 hours. In addition, assessment was made immediately before dosing in the morning for the previous 30 minutes. Total symptom score was calculated as the sum of scores for the 4 individual symptoms: (1) sneezing, (2) rhinorrhea, (3) itchy nose, palate, or throat, and (4) itchy, watery, or red eyes; the nasal congestion score was also recorded. **RESULTS:** Both doses of fexofenadine HCl were superior to placebo in reducing the total symptom score. Efficacy was maintained for the entire dosing interval (ie, for 24 hours). There were no differences in efficacy between the 2 doses of fexofenadine HCl or between either dose of fexofenadine HCl and cetirizine. There was no major side effect, but the combined incidence of drowsiness or fatigue was greater with ce-tirizine (9%) than with placebo (4%) ($P = .07$) or fexofenadine (4%) ($P = .02$). **CONCLUSIONS:** Once-daily fexofenadine is thus a valuable addition to the nonsedating group of H₁ receptor antagonists currently available for the treatment of seasonal allergic rhinitis.

Allergy Asthma Proc. 1998 May-Jun;19(3):135-41.

Effectiveness and safety of fexofenadine, a new nonsedating H₁-receptor antagonist, in the treatment of fall allergies.

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Fexofenadine HCl is a new, nonsedating H₁-receptor antagonist approved for treatment of seasonal allergic rhinitis (SAR). In a double-blind, randomized, placebo-controlled, multicenter trial, 588 patients with fall SAR rated the severity of their symptoms using a scoring system at a screening visit and during a 3-day placebo lead-in period. Patients who did not respond to placebo and met symptom severity criteria were randomized to receive placebo or fexofenadine HCl at 40, 60, or 120 mg bid at 7:00 a.m. and 7:00 p.m. for 14 days. Patients continued to rate the severity of their symptoms immediately before receiving each dose (at trough). A total of 545 patients were included in an intent-to-treat analysis. The change from baseline in the primary efficacy variable (average daily 7:00 p.m. reflective symptom scores) was significantly greater in patients receiving all dosages of fexofenadine HCl than placebo ($p < 0.01$). All active dosages produced significant decreases ($p < 0.05$) in secondary end points: 7:00 a.m. reflective symptom scoring; 7:00 a.m. and 7:00 p.m. scoring 1-hour before dose; and bedtime scoring 1-3 hours after the 7:00 p.m. dose. All dosages of fexofenadine HCl were well tolerated, and no effect on QTc was observed. In conclusion, fexofenadine HCl is safe and effective in the treatment of fall SAR, with 60 mg bid being the optimal therapeutic dosage.

Ann Allergy Asthma Immunol. 2003 Jun;90(6):629-34.

Relative potency of fexofenadine HCl 180 mg, loratadine 10 mg, and placebo using a skin test model of wheal-and-flare suppression.

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BACKGROUND: H1-receptor antagonists differ in their ability to produce peripheral H1-blockade. Suppression of histamine-induced flares and wheals is a useful objective test for measuring these differences. **OBJECTIVE:** To evaluate the relative potency of fexofenadine HCl 180 mg, loratadine 10 mg, and placebo (PBO) in suppressing histamine-induced flares and wheals and compare the onset, duration, and maximum suppression of histamine achieved with each agent. **METHODS:** Thirty healthy volunteers were enrolled in this randomized, double-blind, single-dose, crossover study. Flares and wheals induced by skin-prick testing with histamine 1.8 mg/mL were measured before treatment, every 20 minutes during the first hour after dosing, and thereafter hourly between 2 and 12 hours and between 23 and 25 hours postdose. **RESULTS:** Fexofenadine was significantly more effective than loratadine in suppressing the histamine-induced flare response at hours 2 through 7 and 10 through 12 and produced greater flare suppression than did PBO at hours 2 through 25. Onset of flare suppression occurred 2 hours after dosing with fexofenadine and 4 hours after dosing with loratadine. Likewise, fexofenadine was superior to loratadine in suppressing the wheal response from hours 1 through 12 and was more effective than PBO at hours 1 through 12, 24, and 25. Throughout the 25-hour measurement interval, the magnitude of difference in both wheal and flare suppression consistently favored fexofenadine over loratadine. **CONCLUSIONS:** In a skin test model of wheal-and-flare suppression, fexofenadine showed rapid distribution into the skin compartment with faster onset of action and greater potency vs loratadine.