Pharmacy Benefits Management Strategic Healthcare Group
Medical Advisory Panel
Drug Class Review: Non-sedating Antihistamines

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Objectives

To review the efficacy, safety, and administration of currently available non-sedating antihistamines in the treatment of allergic rhinitis (AR) and chronic idiopathic urticaria (CIU).

Brand Name	Zyrtec	Allegra	Claritin
Generic Name	Cetirizine	Fexofenadine	Loratadine
Manufacturer	Pfizer	Hoechst Marion Roussel	Schering

I. Introduction

Allergic rhinitis (AR) is a condition that affects about 20% of the American population and is the sixth most prevalent chronic illness. Although not associated with significant mortality, allergic rhinitis has a large impact on morbidity in terms of interference with normal daily activities, lost work and school days and an overall decrease in quality of life. In 1980, AR accounted for 3.5 million lost workdays and more than 150 million dollars in lost wages. Allergic rhinitis is associated with a classic group of symptoms including runny nose, sneezing, itchy and watery eyes, nose and throat. These symptoms may occur during certain seasons of the year such as fall and spring which is known as seasonal allergic rhinitis (SAR). Perennial allergic rhinitis (PAR), on the other hand, occurs all year long and is associated with non-seasonal allergens. The agents most commonly used to treat both types of AR are the antihistamines. [1]

Chronic idiopathic urticaria (CIU) is defined as the occurrence of wheals for a duration of at least 6 weeks and is estimated to occur in 0.1 to 3% of the population. Its primary manifestation is smooth, edematous wheals surrounded by a red flare. The presence of wheals is accompanied by intense itching and is associated with high morbidity. [2]

Histamine plays an important role in the pathophysiology of allergic rhinitis and chronic idiopathic urticaria. This mediator is found in its highest concentrations in the lungs, mast cells, and basophils. Exposure to a sensitizing allergen results in the attachment of IgE molecules to the cells causing release of histamine and other inflammatory mediators. The actions of histamine at the H-1 receptor produce the classic symptoms of an allergic response: pruritus, wheal and flare reactions of the skin; bronchoconstriction and mucus production in the lungs; irritation and congestion in the nose. [3]

Antihistamines were developed as receptor antagonists to block histaminic activity at the H-1 receptor. They are categorized as first or second-generation classes. First-generation antihistamines such as triprolidine, diphenhydramine, chlorpheniramine, clemastine, or hydroxyzine may cause somnolence, central nervous (CNS) system dysfunction, and anticholinergic side effects. The second-generation antihistamines, also known as the nonsedating antihistamines, were created to minimize these side effects and include astemizole, terfenadine, loratadine, cetirizine, and fexofenadine (metabolite of terfenadine). The possibility of serious cardiovascular events has led to the removal of terfenadine and astemizole from the market. Although fexofenadine is a major metabolite of terfenadine, adverse cardiovascular events have not been associated with fexofenadine administration. Therefore, this review will focus on fexofenadine, cetirizine and loratadine. Studies that involve comparison with terfenadine are included because it is considered an effective antihistamine and comparability to other effective agents provide valuable information as to fexofenadine's efficacy.

II. Pharmacology

The classic or first-generation antihistamines are characterized as non-specific due to their additional activity at dopaminergic, serotonergic and cholinergic sites. The chemical structure of these classic agents confers lipophilicity and therefore, allows penetration across the blood brain barrier resulting in clinical adverse effects on the central nervous system such as somnolence, central nervous (CNS) system

dysfunction, and anticholinergic side effects. The development of second-generation antihistamines has focused on greater peripheral H-1 receptor selectivity and decreased lipophilicity in order to minimize unwanted adverse effects. The use of these agents is therefore, preferred in patients that cannot tolerate the adverse effects of the first-generation agents. [3,4]

Although specific for the peripheral H-1 receptor, some of the second-generation antihistamines, such as cetirizine, loratadine, and fexofenadine, may have additional activity at cells involved in the inflammatory response. [3,5,6,7] These actions include possible inhibition of mediator release from mast cells, action on leukotrienes and prostaglandins involved in the late phase allergic response. Lastly, actions may include prevention of expression of the intracellular adhesion molecule-1 (ICAM-1) involved in accumulation of migratory cells at sites of inflammation. [3,5, 6, 7]

III. Indications:

TABLE 1. FDA Approved Indications for Second-Generation Antihistamines

Indication	Cetirizine	Fexofenadine	Loratadine
Seasonal AR	X	X	X
Perennial AR	X		
CIU	X	NDA submitted 7/98	X
Pediatric AR or CIU	SAR/PAR/CIU 2 years of age and older	NDA submitted 7/98 for SAR and CIU 6 to 11 years of age	SAR and CIU 6 years of age and older

AR-allergic rhinitis, SAR-seasonal allergic rhinitis, PAR-perennial allergic rhinitis, CIU-Chronic idiopathic urticaria, NDA-new drug application.

IV. Pharmacokinetics/ Pharmacodynamics [6,7, 8, 9, 10, 11, 12, 13, 14]

The three agents under review differ in their pharmacokinetic and pharmacodynamic properties. The duration of antihistaminic activity is not based entirely on serum half-life because of the presence of active metabolites and high tissue to plasma concentrations. A prolonged duration of action allows for once daily dosing for all agents except fexofenadine. The use of once daily fexofenadine in allergic rhinitis, however, is currently under study. A new drug application was filed with the FDA July, 1998. The following table provides a comparison of various pharmacokinetic and pharmacodynamic properties of the three agents.

TABLE 2: Comparison of Pharmacokinetic and Pharmacodynamic properties of the Second-Generation Antihistamines

Property	Cetirizine	Fexofenadine	Loratadine
Tmax (h)	1	1.3	1.3
Onset (h)	1	1	1-4
Duration (h)	24	12	24
Activity of metabolite	None	None	Descarboethoxyloratadine = 4x parent
T1/2- parent (h)	8.3	14.4	8.4
T1/2 – metabolite (h)	-	-	28
Metabolism	Minimal Hepatic	Minimal Hepatic	Hepatic – 3A4 and 2D6
Elimination	70% urine, 50% unchanged 10% feces	80% feces 12% urine	40% urine 42% feces

V. Clinical Efficacy

Antihistaminic activity is most commonly evaluated by measuring time to onset and duration of suppression of the wheal and flare skin reaction after an epicutaneous histamine injection. All second-generation antihistamines suppress this reaction to varying degrees. However, the clinical value of this test has been questioned and therefore, subjective patient assessment is more commonly used to assess clinical efficacy in both AR and CIU. [15]

Cetirizine, is currently indicated for treatment of chronic idiopathic urticaria, seasonal and perennial allergic rhinitis. Fexofenadine is indicated for seasonal allergic rhinitis and is currently under review for treatment of CIU. Loratadine is indicated for seasonal allergic rhinitis and chronic idiopathic urticaria. With the exception of fexofenadine, many comparative studies have been conducted among the non-sedating antihistamines. Presented in Table 3 are those studies for seasonal and perennial allergic rhinitis as well as the placebo-controlled studies evaluating the efficacy of fexofenadine.

The primary efficacy parameter evaluated in these studies is subjective patient assessment of a group of symptoms including itchy eyes, tearing eyes, redness of eyes, itching ears, sneezing, nasal itching, nasal stuffiness, and nasal discharge. Symptoms are rated, on a four point numerical scale ranging from 0 to 3 (0 = no symptoms; 1 = mild, not bothersome; 2 = moderate, bothersome but not disabling; 3 = severe, disabling). Efficacy is determined by comparing treatment groups in terms of a decrease in symptom score from baseline. Since the second-generation antihistamines are reported to cause less sedation and anticholinergic effects, the occurrence of these events in the studies is listed if provided by the authors.

TABLE 3: Efficacy of Second-Generation Antihistamines in Seasonal and Perennial Allergic Rhinitis

Study/ Indication	Study Design	Sampl Size	Treatment Groups	Duration	Results [a]	Adverse Events
Renton, et al. [16] Perennial AR (Merrell Dow Pharm)	Double – blind Crossover	60	Ter 120mg qd Cet 10mg qd	3 wks each treatment/ total: 6 wks	Cet = Ter	Somnolence: Cet: 7% Ter 0%
Crawford, et al. [17] Perennial AR	Open label Crossover	14	Ter 60mg bid Ast 10mg qd Lor 10mg qd Chlor 8mg bid	Sequential 2wk trial of each drug; no washout; ast given last	Ter = Ast = Lor = Chlor	Somnolence: Chlor (28.5%)> Lor (7%)> Ter (7%)> Ast (0)
Backhouse, et al. [18] Seasonal AR (Merrell Dow Pharm)	Double –blind Randomized	285	Cet 10mg qd Ter 120mg qd	1 week	Cet = Ter Improvement in Symptoms: ~50%	Somnolence: Cet >Ter
Caiafffa, et al. [19] Seasonal AR	Multicenter, Double blind Randomized	142	Ter 120mg qd Cet 10mg qd	1 week	Cet = Ter Improvement in Symptoms: Ter: 46-49% Cet: 40-55 %	Somnolence: Cet>Ter
Meltzer, et al. [20] Seasonal AR (Pfizer)	Double blind Randomized Outdoor park Study	279	Cet 10mg qd Lor 10mg qd Placebo qd	2 days	Cet > Lor = Pla	Somnolence: Cet: 12.9% Lor: 5.4% Pla: 2.2%
Day, et al. [21] Seasonal AR (Pfizer)	Double blind Randomized Allergen Exposure unit Setting	202	Cet 10mg qd Lor 10mg qd Placebo qd	2 days	Cet > Lor = Pla Symptom reduction: Cet: 36.7% Lor: 15.4% Pla: 12% Global assessment: Cet = Lor = Pla	Headache: Lor: 33% Cet: 27% Pla: 28% Fatigue: Cet: 3% Lor: 1.5% Pla: 0%
Howarth, et al. [22] Seasonal AR (Janssen Phar)	Double blind Randomized Placebo Controlled	90	Ter 60mg bid Ast 10mg qd Placebo	8 weeks	Ast > Ter Ast > Pla	Somnolence/ Dry mouth: Ast = Ter = Pla

[a] results reflect conclusions made by authors based on statistical comparisons

[b] Pla = placebo; Lor = loratadine; Cet = cetirizine; Ast = astemizole; Fex = fexofenadine; Ter = terfenadine; Cle = clemastine (first- generation); Chlor = chlorpheniramine (first-generation)

TABLE 3 continued: Efficacy of Second-Generation Antihistamines in Seasonal and Perennial Allergic Rhinitis

Study/ Indication	Study Design	Sampl Size	Treatment Groups	Duration	Results	Adverse Events
Dockhorn, et al. [23] Seasonal AR	Double blind Randomized Placebo Controlled	321	Lor 10mg qd Cle 1mg bid Placebo	14 days	Lor = Cle > Pla Symptom reduction: Lor: 52% Cle: 50% Pla: 28%	Somnolence: Lor: 6.3% Cle: 21.1% Pla: 3.6% Dry mouth: Lor = Cle= Pla
Del Carpio, et al. [24] Seasonal AR	Double blind Randomized Placebo Controlled	309	Lor 10mg qd Ter 60mg bid Placebo	14 days	Lor = Ter > Pla Symptom improvement Lor: 46% Ter: 44% Pla: 35%	Somnolence: Lor: 9.5% Ter: 6.5% Pla: 7.6% (NS) Dry mouth: Lor= Ter= Pla
Chervinsky, et al. [25] Seasonal AR (Schering-Plough)	Double blind Randomized	167	Lor 10mg qd Ast 10mg qd	2 months	Lor = Ast	Somnolence: Lor: 15% Ast: 18% (NS) Dry Mouth: Lor = Ast
Day, et al. [26] Seasonal AR (Nordic Merrell Dow)	Double blind Randomized Placebo Controlled Allergen Exposure unit	111	Ter 60mg Ast 10mg Cet 10mg Lor 10mg Placebo	Single dose	Relative efficacy/ % of pts with definitive relief: (best to worst) Cet> Ter > Lor> Ast>Pla	Somnolence: Ast> Cet = Pla > Ter = Lor
Bernstein, et al. [27] Seasonal AR (Hoechst Marion Roussel)	Double blind Randomized Placebo Controlled	570	Fex 60mg bid Fex 120mg bid Fex 240mg bid Placebo	14 days	Symptom reduction: Fex 60: 28.1% Fex 120: 25.5% Fex 240: 28.1% Pla: 16.9%	Fatigue: Fex 60: 0.7% Fex 120: 0% Fex 240: 1.4% Pla: 0% (NS) Dry mouth: Fex = Pla
Day, et al. [28] Seasonal AR (Nordic Merrell Dow)	Double blind Randomized Placebo Controlled Allergen Exposure unit	99	Fex 60mg Fex 120mg Placebo	Single dose	Fex 60mg > Pla Fex 120mg > Pla	Headache: Fex 60: 12.1% Fex 120: 12.1% Pla: 18.2%
Bronsky, et al. [29] Seasonal AR (Hoechst Marion Roussel)	Double blind Randomized Placebo Controlled	588	Fex 40mg bid Fex 60mg bid Fex 120mg bid Placebo	14 days	Symptom reduction: Fex 40: 21% Fex 60: 21% Fex 120: 25% Pla: 14%	Headache: Fex: 2.5% Pla: 3.4%

[a] results reflect conclusions made by authors based on statistical comparisons

[b] Pla = placebo; Lor = loratadine; Cet = cetirizine; Ast = astemizole; Fex = fexofenadine; Ter = terfenadine; Cle = clemastine (first- generation); Chlor = chlorpheniramine (first-generation). Parenthesis in first column denote industry supported studies.

As seen in the studies described above, the efficacy of the second-generation antihistamines in seasonal and perennial AR are comparable. However, overall efficacy is difficult to compare using these study designs since length of treatment may not be adequate. The methods utilized in the placebo-controlled trials with fexofenadine differ from the active comparative studies. Namely, prior to randomization, all subjects were treated with placebo and those subjects identified as placebo responders were not randomized. This difference may account for the lower percent reductions in symptoms seen in the fexofenadine trials. Although all of the second-generation antihistamines have proven effective compared to placebo, the efficacy of fexofenadine, relative to the other agents in its class, has not been established in direct comparative studies. Its efficacy, however, would not be expected to be different from its parent drug, terfenadine, which is extensively metabolized by the liver. Terfenadine has been shown to have similar efficacy to the other agents in its class. In an abstract by Nsouli, fexofenadine 60 mg bid was compared to loratadine 10 mg qd in patients with seasonal allergic rhinitis. Although no statistical analysis was provided, authors reported symptoms of SAR decreased in 87% of patients taking fexofenadine versus 75% of those taking loratadine. Adverse events were not included in the abstract.[46]

The efficacy of second-generation antihistamines in controlling symptoms of CIU has also been studied. The first-generation antihistamine hydroxyzine is considered the standard of care for treatment of CIU to which other antihistamines are compared. The following table provides a summary of the comparative trials in CIU. Primary efficacy parameters evaluated in these studies include patient and investigator assessment of intensity of itching, size, number, and duration of hives, overall condition and therapeutic response. Symptoms are rated on a four point numerical scale. Efficacy is determined by comparing treatment groups in terms of a decrease in symptom score from baseline and overall response as rated by patient and investigator.

TABLE 4: Efficacy of Second Generation Antihistamines in Chronic Idiopathic Urticaria

Study	Study Design	Sample Size	Treatment Groups	Duration	Results	Adverse Events
Monroe, et al. [30]	Randomized Double blind Placebo Controlled	203	Lor 10mg qd Hyd 25mg tid Placebo	12 weeks	Overall Response: Lor = Hyd > Placebo	Somnolence: Lor: 7% Hyd: 49% Pla: 3% Dry Mouth Lor: 1% Hyd: 13% Pla: 1%
Breneman, et al. [31] (Pfizer Labs)	Randomized Double blind Placebo Controlled	188	Cet 10mg qd Hyd 25mg tid Placebo	4 weeks	Cet = Hyd > Pla	Somnolence: Cet: 15% Hyd: 22% Pla: 5%
Finn,et al. [32] (abstract) (Hoechst Marion Roussel)	Randomized Double blind	439	Fexofenadine 20, 60, 120, or 240 mg bid Placebo bid	4 weeks	Overall response: Fexofenadine (all doses) >Pla (p=0.0001) Doses of 60 mg bid or higher (120-240 mg bid) were most effective	Somnolence: Not noted
Guerra, et al. [33]	Randomized Double blind Placebo Controlled	116	Lor 10mg qd Cet 10mg qd Placebo	4 weeks	Overall response: Lor = Cet > Pla	Somnolence: Lor: 10% Cet: 12% Pla: 8%
Breneman et al [34] (Pfizer Labs)	Randomized Double blind Placebo Controlled	187	Cet 10mg qd Ast 10mg qd Placebo	4 weeks	Onset: Cet > Ast Symptom reduction: Cet = Ast > Pla	Somnolence: Cet: 15% Ast: 10% Pla; 3%
Belaich et al [35]	Randomized Double blind Placebo Controlled	172	Lor 10mg qd Ter 60mg bid Placebo	4 weeks	Symptom reduction: Lor = Ter > Pla	Somnolence: Lor = Ter = Pla

a Hyd = hydroxyzine; Diph = diphenhydramine; Lor = loratadine; Cet = cetirizine; Ast = astemizole. Parenthesis in the first column denote industry supported study.

As seen in the studies described above, the efficacy of loratadine and cetirizine are comparable to hydroxyzine in controlling symptoms of CIU as evaluated by both patient and investigator. The frequency of somnolence and dry mouth in these studies, however, was lower with the second-generation antihistamines. As far as treatment of CIU with fexofenadine, a new drug application was filed in July of 1998. In the application, two clinical trials were described in which fexofenadine provided relief at a minimum dose of 60 mg bid.

VI. Safety and Side Effects of Non-sedating Antihistamines

The most severe adverse effect of second-generation antihistamines is torsades de pointes (TdP). Torsades is a polymorphic ventricular tachycardia that occurs in the setting of marked prolongation of the QT interval.[36, 37] This adverse effect can occur as a result of combining terfenadine or astemizole with drugs (erythromycin, ketoconazole, clarithromycin, nefazodone, etc) known to inhibit their metabolism via the cytochrome P-450 3A4 enzyme system (CYP3A4). Inhibition of CYP3A4 leads to increased levels of terfenadine and astemizole and their metabolites producing quinidine like effects and cardiac toxicity. Because of their potential cardiac toxicity, terfenadine and astemizole have been removed from the market. CYP3A4 inhibitors also decrease loratadine's metabolism. However, no reports of cardiac toxicity have been documented since loratadine does not delay cardiac repolarization like terfenadine and astemizole can.

Higher serum concentrations of loratadine can increase sedation and central nervous system adverse effects. To date, no cardiac events have been reported with fexofenadine or cetirizine.

The second-generation antihistamines still have the ability to cause central nervous system side effects such as sedation; however, the chance is significantly lower than those produced by the first-generation H_1 antagonists. Other side effects occurring less frequently include dry mouth, hypotension, weight gain, and gastrointestinal side effects. [38]

Table 5. Clinical Trials of Electrocardiographic Effects of Second-Generation Antihistamines

Reference	Study Design	N	Agents compared and Duration	Results
Abajo FR, et al.[39] 1999	Cohort study	Acr n=1387 Ast n= 13,154 Cet n= 22,136 Lor n= 33,028 Ter n= 145,398. Avg. of 2.6 RXs/pt	Data collected Jan 1992-Sept 1996.	Nine cases of arrhythmias occurred. The significant relative risks were for Ast (RR=19;95%CI:4.8-76), Cet (RR=7.9;95%CI:1.6-39.3) and Ter (RR=2.1;95%CI:0.5-8.5).
Pratt CM, et al.[40] 1999	DB, R, PC	n= 870 Fex n= 290 Pla	Fex 40, 60, 120, 240mg daily or Pla x 2 weeks	No statistically significant increases in mean QTc in Fex vs. PLB. 6.1% fex vs 6% PLB had QTc > 440 ms with an increase of > 10 ms from baseline.
Pratt CM, et al.[40] 1999	P, PC	Fex n=233 Pla n=231	Fex 240mg daily x 12 month or Pla	No statistically significant increases in mean QTc in Fex vs. Pla were found. 9.9.% Fex vs 9.5% Pla had QTc > 440 ms with an increase of > 10 ms from baseline.
Carr RA, et al.[41] 1998	R, CO	n=24 for Lor and Clar	10 mg Lor daily or 500 mg q 12h of Clar, or both for 10 days, washout for 14 days and crossed over	The increase of Cmax of Lor in combination therapy ranged from -33 to +227% and the AUC 0-24 ranged from –18 to + 423% vs monotherapy. No cardiac events occurred for any patient.
Sale ME, et al.[42] 1994	DB, P, CO	n= 21 for Cet 20, 60mg and Pla	2 day baseline phase, 7 day treatment phase (Cet 20mg, 60mg CET, or Pla), 5 day washout phase, and then crossed-over	No significant prolongation of the QT interval was detected during the study. 4/21 in the 20mg arm and 6/21 in the 60mg arm had increase of 10% (p>0.5)
Pfizer Inc, data on file.[43]	R, CO	n= 16	Arm one: Pla x 1day, Cet 20mg x 5 days, then Ery 500mg tid and Cet 20mg x 10 days. Arm two: Pla x 1 day, Ery 500mg tid x 5 days, then Ery 500mg tid and Cet 20mg x 10 days	
Brennan MD, Et al.[44] 1995	DB, CO	n=22	Lor 10mg + 500mg Ery tid, Lor 10mg + Pla, or Pla + Ery 500mg tid for 10 days	No significant prolongation of the QTc interval was detected during the study between the three groups. No QTc increased more than 8% from baseline or 435 sec.
Affrime MB, et al. 1993[45]	R, DB	n=70	Lor n=50 received 40mg daily for 90 days, Pla n= 20 for 90 days	Compared to baseline no stat sig changes for any ECG parameter. No episodes of dizziness, syncope, or ventricular tachycardias occurred.

R= randomized, DB = double-blind, PC = placebo-controlled, P= parallel, Fex= fexofenadine, Lor= loratadine, Pla= placebo, Acr= acrivastine, Ast= astemizole, Cet= cetirizine, Ter = terfenadine, Clar = clarithromycin, Ery= erythromycin

Drug interactions

The peripheral H-1 receptor blocking agents or second-generation antihistamines do not worsen the central nervous system side effects when used in combination with alcohol or other CNS active drugs.[38] However, in 2 studies, a single dose of cetirizine 10 mg affected driving performance similar to that seen with alcohol. In addition, the effects of alcohol and cetirizine may be additive.[47,48]

Cetirizine: No significant drug interactions have been seen with low dose theophylline, azithromycin, pseudoephedrine, ketoconazole, or erythromycin. A 16% decrease in metabolism of cetirizine was observed with a dose of theophylline 400 mg. It is unknown whether higher doses of theophylline may decrease clearance of cetirizine further.[8]

Fexofenadine: In 2 separate studies, fexofenadine 120 mg bid was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg qd for 7 days. Peak plasma concentrations and area under the curve for fexofenadine increased, but no difference in adverse effects or QTc interval was noted in the individuals receiving erythromycin or ketoconazole plus fexofenadine compared to those taking fexofenadine alone. [11]

Loratadine: Significant increases in plasma concentrations of loratadine were observed after co-administration with usual doses of erythromycin, cimetidine and ketoconazole. Although concentrations of loratadine and its metabolite were increased, no clinically significant changes in QTc interval, EKG, or adverse effects were seen.[9]

Central Nervous System Side Effects (CNS)

When compared to placebo, loratadine and terfenadine demonstrate no greater tendency toward sedation, cognitive or psychomotor impairment. However, results with cetirizine are less conclusive. Several studies suggest that some degree of sedation or impairment of psychomotor function occurs in conjunction with the use of cetirizine. In fact, in 1993, the Pulmonary-Allergy Drugs Committee of the US Food and Drug administration concluded that "the sedative effects of cetirizine are similar to those of the first-generation antihistamines[49,51]" Cetirizine's package insert includes a warning about somnolence and the danger of driving a car or other machinery while using it. In addition, the insert warns about the concomitant use of alcohol or other CNS depressant with cetirizine.

Fexofenadine did not impair psychomotor performance in standardized driving tests at doses up to 240mg daily.[14] Loratadine at a dose of 10-20 mg/day did not impair psychomotor performance as assessed by sleep latency, symbol copying, digit symbol substitution and dynamic visual acuity. Some CNS impairment was observed at a dose of 40 mg daily.[7] Cetirizine 5, 10, or 20mg did not significantly affect assessments of drowsiness or cognitive function, but the 20 mg dose did cause more drowsiness than placebo in several cases.[6] In one study utilizing multiple sleep latency testing (MSLT), diphenydramine was compared to loratadine, cetirizine and placebo. The decrease in sleep latency (increased sleepiness) seen with diphenhydramine reached statistical significance compared to placebo and loratadine but not cetirizine. The authors concluded that the sedative effect of cetirizine, in this study, was considered equal to diphenhydramine[50] Single doses did not appear to affect simulated driving, assembly line, and psychometric performance. Somnolence was the most common reported adverse effect with cetirizine, which appears to be dose-related. [8]

The FDA has allowed manufacturers of fexofenadine and loratadine to use the term **"nonsedating"** in their advertising. However, the makers of cetirizine cannot use the nonsedating claim in their advertising since the incidence of somnolence is twice that seen with placebo. The Federal Aviation Administration, Navy

and US Air Force approved the use of fexofenadine or loratadine by their aviators and flight crews. Cetirizine was not approved for use by these individuals because of its potential for sedation.

TABLE 6. Percent of Patients reporting side effects [8, 9, 10, 11]

	Cetirizine	Placebo	Fexofenadine	Placebo	Loratadine	Placebo
N	2034	1612	679	671	1926	2545
Somnolence/drowsiness	13.7	6.3	1.3*	0.9	8	6
Dry mouth	5	2.3	<1	<1	3	2
Fatigue	5.9	2.6	1.3	0.3	4	3
Dizziness	2	1.3	<1	<1	NR	NR
% withdrawn	2.9	2.4	2.2	3.3	2	2

*****Not dose-related

VII. Dosing and Administration [8,9,10,11]

Drug	Usual dose	Renal dysfunction	Hepatic Dysfunction
Cetirizine	5mg or 10mg daily	CrCl =11-31 ml/ min and hemodialysis pts: 5mg daily	5mg daily
Fexofenadine	60mg twice daily	CrCl <80 ml/min and hemodialysis pts: 60mg daily	No recommendation
Loratadine	10mg daily	CrCl < 30 ml/ min: 10mg every other day	10mg every other day

VIII. Monthly Cost

Drug	Dose	Monthly Cost ($)
Cetirizine	10 mg qd	31.40
Fexofenadine	60 mg bid	31.26
Loratadine	10 mg qd	34.76

IX. Conclusions/ Recommendations

Based on comparative and placebo-controlled studies, the efficacy of loratadine, cetirizine and fexofenadine can be considered superior to placebo and similar to each other. The differences between these agents lie in their pharmacokinetic and pharmacodynamic properties, side effects, drug interactions, administration and cost. Of the three agents, loratadine is metabolized by Cytochrome P450 3A4 isoenzyme (CYP3A4) system and has significant increases in AUC with certain CYP3A4 inhibitors. According to loratadine's package insert, the occurrence of somnolence increases with doses two to four times the recommended dose. All agents can be taken once daily, with the exception of fexofenadine. However, the manufacturers of fexofenadine have filed a NDA with the FDA for once daily dosing of their product for SAR. Cetirizine is associated with dose-related somnolence and cannot be referred to as nonsedating in its advertising claims. Its package insert warns patients against driving or operating machinery while taking cetirizine. The main goal for choosing a second-generation antihistamine is to limit the potential for sedation and somnolence seen with first-generation antihistamines, which can occur in approximately 20 % to 50 % of patients in the first few days of therapy. Therefore, since the safety and efficacy of fexofenadine and loratadine are comparative, the decision between these two agents for addition to the VA National Formulary should be based upon cost.

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