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October 4, 2000

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-21)
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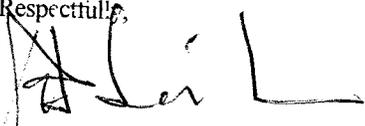
Dear Ms. Ortega:

The undersigned submits this amendment to petition docket number 98P-0610/CP, under the Code of Federal Regulations, Food and Drug Administration, Title-21, section 10.30. This regulation provides that drugs limited to prescription use under an NDA can be exempted from that limitation if the FDA determines the prescription requirements to be unnecessary for the protection of public health. By receipt of this letter, I am submitting an Evidence Report that compares the safety and efficacy of the first generation (cough-hydramine, chlorpheniramine) and second generation antihistamines (cetirizine, loratadine, and fexofenadine) for the treatment of allergic rhinitis.

Sedation, driving impairment, and life-threatening cardiac arrhythmias are the important adverse effects associated with antihistamines. The Evidence Report documents that the incidence of sedation, driving impairment, and life-threatening cardiac arrhythmias are significantly higher with the first-generation antihistamines than the second-generation antihistamines. It also documents that the efficacy of the first and second-generation antihistamines for the treatment of allergic rhinitis is comparable. Since the second-generation antihistamines are less toxic and equally efficacious as the first generation antihistamines, the second-generation antihistamines are the preferred antihistamine treatment for allergic rhinitis.

This Evidence Report has been submitted under current FDA regulations that provide that drugs limited to prescription use under an NDA can be exempted from that limitation if the FDA determines the prescription requirements to be unnecessary for the protection of public health. Please expedite the FDA review of petition docket number 98P-0610/CP, requesting the conversion of cetirizine, loratadine and fexofenadine to over-the-counter medication status immediately.

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

Respectfully,

Robert Seidman, PharmD, MPH

cc: Douglas Schur, Vice President of Legal Services
David T. Read, Esq., U.S. F.D.A. C.D.E.R.
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SUP 2

Evidence Report: Second Generation Antihistamines versus First Generation Antihistamines for the Treatment of Allergic Rhinitis

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Introduction:

This is an Evidence Report to compare the safety and efficacy of the first generation (diphenhydramine, chlorpheniramine) and second generation antihistamines (cetirizine, loratadine, fexofenadine) for the treatment of allergic rhinitis.

Table 1. Generic, Trade Name and Manufacturer

Generic	Trade Name	Manufacturer
Diphenhydramine	Benadryl	Parke-Davis
Chlorpheniramine	Chlor-Trimeton	Schering-Plough Healthcare
Cetirizine	Zyrtec	Pfizer
Loratadine	Claritin	Schering
Fexofenadine	Allegra	Hoechst-Marion Roussel
Terfenadine	Seldane (discontinued)	Hoechst-Marion Roussel

Methods:

The literature search was conducted to identify all randomized controlled trials (RCT), reviews, and meta-analysis associated with cetirizine, loratadine, fexofenadine, diphenhydramine and chlorpheniramine.

Three literature databases were searched: MEDLINE (1966-June 2000), BIOSIS (1970-June 2000) and Cochrane Controlled Trials Registry (1980-June 2000). Searches were limited to the English language.

Two hundred and eighty-nine titles were identified. These titles and abstracts were screened by two literature reviewers. The inclusion criteria were rhinitis, cellular response, adults, children, reviews, meta-analysis, and one of the above antihistamines compared with placebo. One hundred and ninety-two references were excluded

Ninety-seven articles were photocopied, screened and reviewed. After review of these 97 articles the inclusion criteria evolved to include articles with a focus of seasonal or perennial rhinitis, adults, children, comparison of cetirizine, loratadine, fexofenadine, diphenhydramine, chlorpheniramine and placebo, performance, reviews and meta-analysis. Articles with a focus of cellular or cutaneous response were excluded because these studies evaluated the cellular response of blocking histamine and the direction of this report is to evaluate the clinical response of the subject. Also, the cellular response was measured by a variety of tests and it would be difficult to pool these results. Of the 97 articles reviewed, 36 comparative RCTs (34 articles¹⁻³⁴ reference 27 described 3 RCTs in the single reference), 1 performance³⁵ and 8 review articles³⁶⁻⁴⁴ have been selected. The data for the evidence tables are from these 34 RCT articles.

A computer database (Access[®]) was developed to organize and control the evidence-based process. As the articles were reviewed, data were entered into the database.

Evidence Tables (Appendix A):

Ref Num/Author/Source/Year:

The primary author, journal and year published are included in the tables to give a sense of the source of the data.

Design/Population:

The quality of the study is described by evaluating four characteristics. The preferred randomization process is when the investigators use a third party to implement a computer or envelope system to assign an empanelled subject to a treatment arm. The assignment of subjects to a treatment arm was concealed if a third party was employed to assign a subject to a treatment group. Because of the subjective nature of the outcomes for the treatment of rhinitis, double blinding was necessary. The intent to treat analysis was adequate if the investigators described the number of subjects empanelled into the study, the number of subjects available for evaluation and then accounted for the difference between the empanelled subjects and those remaining for evaluation. If the authors did not describe these processes, then it is assumed that they did not employ the preferred method and the study design was not optimal but acceptable.

Twenty-one of the 36 RCTs did not adequately describe the randomization process. They simply stated that the design had included randomization. None of the RCTs described the concealment process. It was not clearly stated whether the investigators had knowledge of randomization sequence. However, only 3 of the 36 RCTs failed to describe the blinding process of the study. Because of the subjective nature of the outcome data, the double blinding of the studies is very important. Nine of the 36 RCTs did not provide details of the patients who were excluded or dropped from the study. The quality of this pool of studies is acceptable and sufficient to use for policy decisions.

The population is an important source of heterogeneity. We included only studies of perennial or seasonal rhinitis of adults (32 RCTs) or children (4 RCTs). Twenty-nine of the RCTs were on subjects who suffered from seasonal rhinitis. Twenty-one of the 29 studies were conducted during the allergy season. Eight studies (Study 30 included both seasonal and perennial subjects) selected subjects with perennial rhinitis and none of these studies were conducted during a particular season of the year. Most of the studies required that the subjects have a history of rhinitis for at least 2 years and a positive skin test for allergy. The antigen source was either from natural exposure (33 RCTs) to the environment or induced by placing the subject in a controlled chamber (3 RCTs)^{6,9,26} and exposing them to a measured quantity of antigen. Seven of the studies report a pollen count. Two studies (4, 35) describe frequent pollen counts during the study period. Backhouse³⁶ clearly showed that during the pollen season, the daily pollen counts can vary considerably (<10 to >200 grains/m³) and a pollen count of 50 or more is generally associated with symptoms in susceptible individuals. In their study, they described a strong correlation between worsening of symptoms and the daily pollen count.

Thirty-two studies included subjects who were greater than 12 years of age and 4 studies included children 2-14 years old. Most of the subjects were less than 65 years of age. All studies welcomed both female and male subjects.

Purpose:

The purpose of the study was included to succinctly describe the nature of the study.

Significant Factors:

Two subjective measurements of efficacy were commonly used in these RCTs: The Total Symptom Score (TSS) and Global Efficacy Evaluation. The TSS method required the subject, parent or physician to collect subjective data on cards at specified times. The symptoms were of the eyes, nose, throat and ears. A range of 5 to 10 symptoms were observed (Table 2). The evaluator scored each symptom on a scale of absent to intolerable. Various scoring systems used a scale of 0 to 4-10 (Table 3). Most studies (25 RCTs) used a 4 point system (0-3).

Table 2. Symptoms

5 Symptoms ⁶	8 Symptoms ⁹	10 Symtoms ⁸
1. Nasal congestion	1. Nasal congestion	1. Nasal Congestion
2. Sneezing	2. Sneezing	2. Sneezing
3. Rhinorrhea	3. Rhinorrhea	3. Rhinorrhea
4. Itchy nose/palate, and/or throat	4. Nasal itching	4. Nasal itching
5. Itchy, watery and red eye	5. Itching of the roof of the mouth	5. Itching throat
	6. Post nasal discharge	6. Itching ears
	7. Lacrimation	7. Erythema ears
	8. Ocular itching	8. Lacrimation
		9. Itching eyes
		10. Red eyes

Table 3. Symptom Score⁶

5 Point Scale
0 = Absent (no symptom)
1 = Mild (symptom is present but is not annoying or troublesome)
2 = Moderate (symptom is troublesome but does not interfering with normal activity)
3 = Severe (symptom is sufficiently troublesome to interfere with normal daily activity)
4 = Very Severe (symptom is so severe that the patient should immediately visit a physician)

Nasal congestion is a symptom that is usually not responsive to an antihistamine. Therefore, some of the scoring systems excluded nasal congestion.

Most often the TSS was collected daily before the next dose by the patient or at an office visit by the investigator. If the evaluator was the patient, the baseline TSS (before drug therapy) was compared with an average TSS collected during drug therapy. The drug therapy collection period varied from 5 hours to 6 weeks. If the evaluator was the physician, the baseline TSS was compared with the TSS collected at a later office visit, usually weekly for 1 to 4 weeks. The drug effect was measured by the decrease in the TSS while receiving therapy compared with the baseline TSS. As described above, the TSS is greatly influenced by the daily pollen count which can vary considerably from day to day. If the pollen count is high on the baseline day, the TSS will be high and if the pollen counts decrease during the subsequent days while the subject is receiving drug therapy the TSS will be low and the reduction in the TSS will be erroneously attributed to a large drug effect. However, if the pollen count is low at baseline and the TSS is low and if the pollen count increases while receiving treatment, then the TSS may decrease very little or may even be higher than baseline and the drug effect will be small or possibly negative. Perhaps a better way to measure the reduction of the TSS is to compare the average TSS of the patients receiving drug therapy to the average TSS of the placebo group. This method will reduce the influence of the daily pollen count on the way the efficacy of therapy is measured. This is the process utilized in this report for the meta-analysis of efficacy measured by the reduction in the TSS.

The Global Efficacy Evaluation measured subjectively the overall relief of rhinitis symptoms. This assessment was done by the physician, patient or parent. The most common scoring scale was 5 points. Zero was associated with complete relief and 1 with marked relief (Table 4). At the end of therapy the evaluator reported the degree of relief. At the completion of the study, the investigators reported the percentage of subjects who experienced complete or marked relief. These are the data that were used in the meta-analysis for the Global Efficacy of the antihistamines.

Table 4. Global Efficacy Evaluation⁶

5 Points
0 = Complete relief (no symptoms were present)
1 = Marked relief (symptoms were vastly improved but occasionally are present)
2 = Moderate relief (symptoms are noticeably improved but are still present)
3 = Slight relief (symptoms are present and only minimal improvement has been established)
4 = No relief (symptoms are unchanged or worse)

The placebo effect for subjects with rhinitis is large. This may be partially explained by the effect of the variation in the daily pollen count. Six of the RCTs used a several day lead-in period on placebo. If during the lead-in period the subject's TSS decreased, the subject was not randomized to the treatment or placebo arms.

Groups/Outcomes:

The drug, dose, frequency, and number of treated and placebo subjects are described under Groups/Outcomes. The Global Response is the number of subjects who reported complete or marked relief of rhinitis symptoms. The percent is the number of responders divided by the

total number of subjects in a group. The symptoms baseline is the baseline symptom score before drug therapy is started. Some of the baseline and symptom score variation between studies may be explained by the different scoring systems used and/or a difference in the degree of rhinitis of the subjects. For the meta-analysis, only the studies that used a 4 point scoring system were combined. The percent reduction is calculated by subtracting the average symptom score of the treated group from the placebo and dividing the difference by the placebo average symptom score. This measures the effectiveness of drug in relationship to the effectiveness of the placebo and reduces the timing associated impact of the pollen count on the efficacy of the drug as seen when measuring the efficacy of the drug by comparing its effect to baseline measurements.

The incidence of sedation is the reported number of subjects complaining of sedation divided by the number subjects in the group. Subjects who reported such complaints as fatigue or tiredness were not included in the sedation incidence. For the meta-analysis the incidence of sedation for the treated group was compared with the placebo group.

The incidence of all adverse reactions was calculated by summing all reported reactions and dividing by the number of subjects. For most reports it was not clear which patients had more than one complaint and the duration of therapy varied from one dose to 42 days. For these reasons the incidence of all adverse reactions was reported for general purposes and not for meta-analysis.

Meta-analysis:

Statistical Analysis:

The 95% confidence intervals were calculated for two proportions and two samples. The meta-analysis summary estimate of difference measure was the general variance-based methods. A level of significance at $p < 0.05$ was used for all comparisons.⁴⁴

Meta-analysis:

When more than three studies comparing the same drug to placebo or other antihistamine of interest for treatment of rhinitis and measured outcomes in a similar fashion were identified, a meta-analysis was performed. The global efficacy of cetirizine and loratadine versus placebo was reported in 7 and 11 studies respectively. The global efficacy of chlorpheniramine versus terfenadine was described in 5 studies. The global efficacy of cetirizine versus loratadine was reported in 3 studies. The global efficacy of cetirizine versus placebo in children was detailed in 3 studies. The total symptom score reduction for cetirizine, loratadine and fexofenadine versus placebo was related in 7, 10, and 4 studies respectively. Sedation was reported for cetirizine, loratadine, and chlorpheniramine in 9, 11, and 6 studies respectively. The incidence of sedation in children receiving cetirizine versus placebo was described in 3 studies.

For each of the comparisons, the point estimate (the difference between the incidence of the treatment group vs the placebo group) and the 95% confidence interval are shown. If the difference between the treatment group and comparison group is statistically significant ($p < 0.05$), the point estimate is greater than zero and the confidence interval will not include the 0.0 line.

Table 5. Meta-analysis Summary of Global Efficacy

Treated Group (n)	Comparison Group (n)	Number of Studies	Overall Effect Size	95% Confidence Interval	p value
Cetirizine 10 mg (384)	Placebo (378)	7	0.24	0.17-0.31	<0.001
Loratadine 10 mg (746)	Placebo (744)	11	0.21	0.16-0.26	<0.001
Cetirizine (Children) (193)	Placebo (197)	3	0.26	0.16-0.36	<0.001
Cetirizine 10 mg	Loratadine 10 mg	3	0.15	0.05-0.25	<0.05
Chlorpheniramine (199)	Terfenadine (203)	5	0.05	-.02-0.12	>0.05

Table 5 summarizes the meta-analysis for the comparisons of cetirizine in adults and children vs placebo, loratadine in adults vs placebo, and chlorpheniramine in adults vs terfenadine. In adults and children the effect size of cetirizine and loratadine vs placebo is very similar, 0.24, 0.26 and 0.22 respectively. This means for the treatment of allergic rhinitis in adults and children approximately 1 in 4 or 25% of the subjects treated with cetirizine or loratadine will experience complete or marked relief of symptoms. When cetirizine and loratadine were compared to each other, cetirizine was more effective. One out of 7 more subjects will respond to cetirizine than loratadine. Fexofenadine was not included in this comparison because only one study has been published that compares fexofenadine vs placebo for global efficacy.

Are second generation antihistamines as effective as first generation antihistamines? We searched the literature for comparisons between first and second generation antihistamines. The only comparison of three or more studies was between chlorpheniramine and terfenadine. The meta-analysis of this comparison demonstrates no statistically significant difference between the first generation antihistamine (chlorpheniramine) and second generation antihistamine (terfenadine). These findings suggest a comparable efficacy between first and second generation antihistamines.

Table 6. Meta-analysis Summary of Total Symptom Score Reduction

Treated Group (n)	Comparison Group (n)	Number of Studies	Overall Effect Size	95% Confidence Interval	p value	% Reduction
Cetirizine 10 mg (555)	Placebo (544)	7	1.87	1.75-1.99	<0.05	27.4
Loratadine 10 mg (612)	Placebo (599)	9	2.8	2.91-2.70	<0.05	34.1
Fexofenadine 120 mg (777)	Placebo (771)	4	0.83	0.81-0.85	<0.05	12.2

Table 6 summarizes the efficacy of cetirizine, loratadine, and fexofenadine vs placebo when measured by the reduction of total symptom score. The effect size is the difference between the placebo group total symptom score minus the treated group total symptom score.

And the percent reduction is the effect size divided by the placebo group total symptom score. All three drugs are more effective than placebo. Loratadine may have the largest effect size because the placebo group had the largest average total symptom score (8.2) which suggests that these patients had more symptoms than the cetirizine or fexofenadine subjects and possibly more of an opportunity for the loratadine to be effective. The average symptom score for the cetirizine and fexofenadine placebo groups was the same (6.8), suggesting that the intensity of rhinitis in these two groups was similar and that cetirizine is more effective than fexofenadine.

Table 7. Meta-analysis Summary of Sedation

Treated Group (n)	Comparison Group (n)	Number of Studies	Overall Effect Size	95% Confidence Interval	p value
Chlorpheniramine (219)	Placebo (217)	6	0.17	0.1-0.24	<0.001
Cetirizine 10 mg (766)	Placebo (756)	9	0.06	0.01-0.11	<0.05
Cetirizine (Children) (163)	Placebo (160)	3	0.05	0.01-0.09	<0.02
Loratadine 10 mg (727)	Placebo (714)	11	0.0	-.02-0.02	>0.05

Table 7 summarizes the incidence of sedation of these antihistamines compared with placebo. The incidence for chlorpheniramine, cetirizine (adults), cetirizine (children), and loratadine is 17%, 6%, 5% and 0% respectively. The incidence of sedation for cetirizine is approximately one third compared with chlorpheniramine. Also the incidence of sedation reported in adult and pediatric subjects was nearly the same. Notably, the incidence of sedation for loratadine is not different than experienced with placebo. Fexofenadine was not included in this table because only one of the five studies that compared fexofenadine with placebo included data describing sedation. The other four studies did not tabulate sedation data because apparently the subjects in either the treated or placebo groups did not complain of sedation.

Performance:

The Federal Aviation Administration does not approve pilots to fly under the influence of first generation antihistamines. If a pilot takes loratadine or fexofenadine for 48 hours, experiences no symptoms of sedation and notes these observations with their physician, the pilot can fly while taking loratadine or fexofenadine. This procedure of notifying a physician applies to the pilot's first exposure to loratadine or fexofenadine. On subsequent incidences, the pilot may take loratadine or fexofenadine and fly if the pilot does not experience symptoms of sedation. For cetirizine, pilots are not approved to fly until 48 hours after their last dose.

Perhaps the best measure of the effect antihistamines have on performance is the Dutch experience. Eight studies have been conducted on first and second generation antihistamines and these findings have been standardized by comparison of impairment with known concentrations of ethanol. The first generation antihistamines (triprolidine, diphenhydramine, and clemastine) tested produced driving impairment associated with ethanol concentrations of 0.5 to 1 mg/ml. These studies used standard doses of the first generation antihistamines. In California it is illegal to drive an automobile with an alcohol concentration of equal or greater than 0.8 mg/ml. No significant driving impairment was noted after a single 10 mg dose of loratadine or after 10 mg daily for 4 days. A slight impairment was observed when the dose was doubled to 20 mg as a

single dose or after 20 mg daily for 4 days. Cetirizine's effect on driving is not clear since the findings from two studies are not consistent. One study found no significant effect with a single daily dose of 10 mg or after four daily doses. The other study demonstrated a significant effect on driving after a single 10 mg dose. The gender composition of the two studies were 27 males in the first study and 8 males and 8 females in the second study. Perhaps there is a gender effect or possibly the 10 mg dose in females has greater effect since the drug is not normalized for weight. Fexofenadine has not been investigated but 4 studies have evaluated terfenadine. When subjects were given 60 mg bid or 120 mg qd no significant impairment in driving was noted. In all three of these studies, driving performance was slightly better in the groups receiving treatment than the placebo. These findings suggest a mild stimulating activity of the drug. In a fourth study, when the dose was increased to 120 mg bid, a slight impairment of driving was observed. In summary, the first generation antihistamines produce driving impairment similar to intoxicating concentrations of alcohol (0.5 to 1 mg/ml) and the second generation antihistamines produce minimal impairment when given standard doses and perhaps minimally significant impairment when given twice the usual daily dose.³⁵

Risk of Ventricular Arrhythmia:

Pratt determined that greater than five million subjects would need to be randomized to provide sufficient power to evaluate the occurrence of terfenadine associated ventricular arrhythmias by means of a randomized study design. Since such a study is not feasible, a retrospective study of the Computerized on-line Medical Pharmaceutical Analysis and Surveillance System has been done. The study included 597,189 subjects. The endpoint was life-threatening ventricular arrhythmias. Terfenadine was compared with ibuprofen, clemastine and other over-the-counter antihistamine cohorts. The relative risk of a life-threatening ventricular arrhythmia was less in the terfenadine group than the ibuprofen or OTC antihistamine groups and not statistically different ($p > 0.05$) than the clemastine group. When terfenadine was compared with a subgroup of subjects who received both terfenadine and ketoconazole, the relative risk of a life-threatening ventricular arrhythmia was highly statistically significant ($p < 0.001$). The OTC antihistamine group consisted primarily of diphenhydramine (94%) and the relative risk of a life-threatening ventricular arrhythmia was statistically significant ($p < 0.001$) compared to terfenadine. In summary, the risk of a life-threatening ventricular arrhythmia is significant when terfenadine is given in combination with a cytochrome P450 inhibitor such as ketoconazole. Also of interest, the relative risk of a life-threatening ventricular arrhythmia is significant when the first generation antihistamine, diphenhydramine, is given.⁴⁵

Loratadine is not associated with cardiac toxicity. The cardiac potassium channel is not compromised with normal or elevated loratadine levels. Loratadine is metabolized by cytochrome P450 CYP3A4 hepatic enzyme which can be inhibited by such drugs as ketoconazole or erythromycin. However loratadine is also metabolized by an alternative enzyme P450 CYP2D6. When P450 CYP3A4 is inhibited, the alternative metabolic pathway, P450 CYP2D6, is utilized and large increases in the serum concentration of loratadine are not observed.⁴⁶

In animal or human studies, cetirizine has not been associated with significant arrhythmogenic effects with normal or high levels. Cetirizine does not block the potassium channel associated with repolarization of the cardiac conduction system. Also, approximately 80% of the absorbed dose is recovered unmetabolized in the urine. Therefore, the inhibition of metabolism by such drugs as ketoconazole or erythromycin is not important.⁴⁶

Torsade de pointes was not observed in any of 6000 subjects who received doses as high as 690 mg bid of fexofenadine during clinical development of the drug. In animal studies, fexofenadine does not block the cardiac potassium channel even when very high doses were given. In clinical trials testing for drug interactions with ketoconazole or erythromycin, the QTc was not prolonged. After extensive evaluation, fexofenadine was not observed to produce cardiotoxicity.⁴⁷

In summary, of all the antihistamines studied extensively, diphenhydramine has the highest incidence of life-threatening cardiac toxicity, higher than terfenadine. Loratadine, cetirizine, and fexofenadine are associated with a cardiac toxicity incidence similar to placebo.

Conclusion:

Sedation, driving impairment, and life-threatening cardiac arrhythmias are the important adverse effects associated with antihistamines. The incidence of sedation, driving impairment, and life-threatening cardiac arrhythmias are significantly higher with the first generation antihistamines than the second generation antihistamines. The efficacy of the first and second generation antihistamines for the treatment of allergic rhinitis is comparable. Since the second generation antihistamines are less toxic and equally efficacious as the first generation antihistamines, the second generation antihistamines are the preferred antihistamine treatment for allergic rhinitis.

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