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of California

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October 4, 2000

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-21)
ATTN: Gloria Ortega
5600 Fishers Lane
Rockville, MD 20857

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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 (diphenhydramine, 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.
Rhonda W. Stover, U.S. F.D.A. C.D.E.R.

98P-0610

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.

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 Symptoms 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	-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.

References

- 1 Rajaram S. Suthakaran C. Pradhan S C. Majumder N K. Bapna J S. Double blind randomized clinical trial of cetirizine in the treatment of perennial allergic rhinitis. *Indian Journal of Pharmacology*. 26(2). 1994. 112-116.
- 2 Falliers CJ. Brandon ML. Buchman E. Connell JT. Dockhorn R. Leese PT. Miller J. Wasserman SI. Zeterberg JM. Altman R. et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. *Annals of Allergy*. 66(3):257-62, 1991 Mar.
- 3 Mansmann HC Jr. Altman RA. Berman BA. Buchman E. Dockhorn RJ. Leese PT. Love SJ. Middleton E Jr. Efficacy and safety of cetirizine therapy in perennial allergic rhinitis. *Annals of Allergy*. 68(4):348-53, 1992 Apr.
- 4 Panayotopoulos SM. Panayotopoulou ES. Efficacy of cetirizine in the treatment of seasonal allergic rhinoconjunctivitis. *Annals of Allergy*. 65(2):146-8, 1990 Aug.
- 5 Wasserman SI. Broide DH. Marquardt DL. Cetirizine therapy for seasonal allergic rhinitis: alternative dosage schedules. *Clinical Therapeutics*. 13(6):707-13, 1991 Nov-Dec.
- 6 Day JH. Briscoe MP. Clark RH. Ellis AK. Gervais P. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 79(2):163-72, 1997 Aug.
- 7 Sabbah A. Daele J. Wade AG. Ben-Soussen P. Alfali P. Comparison of the efficacy, safety, and onset of action of mizolastine, cetirizine, and placebo in the management of seasonal allergic rhinoconjunctivitis. MIZOCET Study Group. *Annals of Allergy, Asthma, & Immunology*. 83(4):319-25, 1999 Oct.
- 8 Lockey RF. Widlitz MD. Mitchell DQ. Lumry W. Dockhorn R. Woehler T. Grossman J. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 76(5):448-54, 1996 May.
- 9 Day JH. Briscoe M. Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *Journal of Allergy & Clinical Immunology*. 101(5):638-45, 1998 May.
- 10 Meltzer EO. Weiler JM. Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 97(2):617-26, 1996 Feb.
- 11 Howarth PH. Stern MA. Roi L. Reynolds R. Bousquet J. 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. *Journal of Allergy & Clinical Immunology*. 104(5):927-33, 1999 Nov.
- 12 Bedard PM. Del Carpio J. Drouin MA. Yang W. Hebert J. Lavoie A. Prevost M. Turenne Y. PetitClerc C. Lorber R. Onset of action of loratadine and placebo and other efficacy variables in patients with seasonal allergic rhinitis. *Clinical Therapeutics*. 14(2):268-75, 1992 Mar-Apr.
- 13 Bruttman G. Charpin D. Germouty J. Horak F. Kunkel G. Wittmann G. Evaluation of the efficacy and safety of loratadine in perennial allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 83(2 Pt 1):411-6, 1989 Feb.
- 14 Bruttman G. Pedrali P. Loratadine (SCH29851) 40 mg once daily versus terfenadine 60 mg twice daily in the treatment of seasonal allergic rhinitis. *Journal of International Medical Research*. 15(2):63-70, 1987 Mar-Apr.
- 15 Del Carpio J. Kabbash L. Turenne Y. Prevost M. Hebert J. Bedard PM. Nedilski M. Gutkowski A. Schulz J. Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 84(5 Pt 1):741-6, 1989 Nov.
- 16 Dockhorn RJ. Bergner A. Connell JT. Falliers CJ. Grabiec SV. Weiler JM. Shellenberger MK. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. *Annals of Allergy*. 58(6):407-11, 1987 Jun.
- 17 Frolund L. Efficacy of an oral antihistamine, loratadine, as compared with a nasal steroid spray, beclomethasone dipropionate, in seasonal allergic rhinitis. *Clinical Otolaryngology & Allied Sciences*. 16(6):527-31, 1991 Dec.

- 18 Gutkowski A. Bedard P. Del Carpio J. Hebert J. Prevost M. Schulz J. Turenne Y. Yeadon C. Comparison of the efficacy and safety of loratadine, terfenadine, and placebo in the treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 81(5 Pt 1):902-7, 1988 May.
- 19 Horak F. Bruttman G. Pedrali P. Weeke B. Frolund L. Wolff HH. Christophers E. A multicentric study of loratadine, terfenadine and placebo in patients with seasonal allergic rhinitis. *Arzneimittel-Forschung*. 38(1):124-8, 1988 Jan.
- 20 Oei HD. Double-blind comparison of loratadine (SCH 29851), astemizole, and placebo in hay fever with special regard to onset of action. *Annals of Allergy*. 61(6):436-9, 1988 Dec.
- 21 Skassa-Brociek W. Bousquet J. Montes F. Verdier M. Schwab D. Lherminier M. Michel FB. Double-blind placebo-controlled study of loratadine, mequitazine, and placebo in the symptomatic treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 81(4):725-30, 1988 Apr.
- 22 Dolovich J. Moote DW. Mazza JA. Clermont A. PetitClerc C. Danzig M. Efficacy of loratadine versus placebo in the prophylactic treatment of seasonal allergic rhinitis. *Annals of Allergy*. 73(3):235-9, 1994 Sep.
- 23 Casale TB. Andrade C. Qu R. Safety and efficacy of once-daily fexofenadine HCl in the treatment of autumn seasonal allergic rhinitis. *Allergy & Asthma Proceedings*. 20(3):193-8, 1999 May-Jun.
- 24 Bronsky EA. Falliers CJ. Kaiser HB. Ahlbrandt R. Mason JM. Effectiveness and safety of fexofenadine, a new non-sedating H1-receptor antagonist, in the treatment of fall allergies. *Allergy & Asthma Proceedings*. 19(3):135-41, 1998 May-Jun.
- 25 Bernstein DI. Schoenwetter WF. Nathan RA. Storms W. Ahlbrandt R. Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 79(5):443-8, 1997 Nov.
- 26 Day JH. Briscoe MP. Welsh A. Smith JN. Clark A. Ellis AK. Mason J. Onset of action, efficacy, and safety of a single dose of fexofenadine hydrochloride for ragweed allergy using an environmental exposure unit. *Annals of Allergy, Asthma, & Immunology*. 79(6):533-40, 1997 Dec.
- 27 Brandon ML. Weiner M. Clinical investigation of terfenadine, a non-sedating antihistamine. *Annals of Allergy*. 44(2):71-5, 1980 Feb.
- 28 Melillo G. D'Amato G. Zanussi C. Ortolani C. Pastorello E. Loy M. Di Tucci A. Locci F. Del Giacco GS. Lenzini L. Sestini P. Rottoli P. A multicentre controlled trial of terfenadine, dexchlorpheniramine, and placebo in allergic rhinitis. *Arzneimittel-Forschung*. 32(9a):1202-3, 1982.
- 29 Brostoff J. Lockhart JD. Controlled trial of terfenadine and chlorpheniramine maleate in perennial rhinitis. *Postgraduate Medical Journal*. 58(681):422-3, 1982 Jul.
- 30 Backhouse CI. Brewster BS. Lockhart JD. Maneksha S. Purvis CR. Valle-Jones JC. Terfenadine in allergic rhinitis. A comparative trial of a new antihistamine versus chlorpheniramine and placebo. *Practitioner*. 226(1364):347-51, 1982 Feb.
- 31 Baelde Y. Dupont P. Cetirizine in children with chronic allergic rhinitis: A multicentre double-blind study of two doses of cetirizine and placebo. *Drug Investigation*. 4(6). 1992. 466-472.
- 32 Jobst S. van den Wijngaert W. Schubert A. van de Venne H. Assessment of the efficacy and safety of three dose levels of cetirizine given once daily in children with perennial allergic rhinitis. *Allergy*. 49(8):598-604, 1994 Sep.
- 33 Masi M. Candiani R. van de Venne H. A placebo-controlled trial of cetirizine in seasonal allergic rhino-conjunctivitis in children aged 6 to 12 years. *Pediatric Allergy & Immunology*. 4(4 Suppl):47-52, 1993.
- 34 Cetirizine for seasonal allergic rhinitis in children aged 2-6 years. A double-blind comparison with placebo. *Pediatric Allergy & Immunology*. 4(3):157-61, 1993 Aug.
- 35 O'Hanlon JF. Ramaekers JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy*. 50(3):234-42, 1995 Mar.
- 36 Backhouse CI. Rosenberg R. Prophylaxis of whole season hay fever symptomatology: a comparison of terfenadine with chlorpheniramine. *British Journal of Clinical Practice*. 41(11):995-9, 1987 Nov.
- 37 Slater JW. Zechnich AD. Haxby DG. Second-generation antihistamines: a comparative review. *Drugs*. 57(1):31-47, 1999 Jan.

- 38 Simpson K. Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs*. 59(2):301-21, 2000 Feb.
- 39 Gonzalez MA. Estes KS. Pharmacokinetic overview of oral second-generation H1 antihistamines. *International Journal of Clinical Pharmacology & Therapeutics*. 36(5):292-300, 1998 May.
- 40 Mattila MJ. Paakkari I. Variations among non-sedating antihistamines: are there real differences?. *European Journal of Clinical Pharmacology*. 55(2):85-93, 1999 Apr.
- 41 Haria M. Fitton A. Peters DH. Loratadine. A reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs*. 48(4):617-37, 1994 Oct.
- 42 Clissold SP. Sorkin EM. Goa KL. Loratadine. A preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. 37(1):42-57, 1989 Jan.
- 43 Spencer CM. Faulds D. Peters DH. Cetirizine. A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs*. 46(6):1055-80, 1993 Dec.
- 44 Barnes CL. McKenzie CA. Webster KD. Poinsett-Holmes K. Cetirizine: a new, non-sedating antihistamine. *Annals of Pharmacotherapy*. 27(4):464-70, 1993 Apr.
- 45 Petitti DB. *Meta-Analysis decision analysis and cost-effectiveness analysis*. Oxford, New York, Oxford University Press, 1994.
- 46 Pratt CM. Hertz RP. Ellis BE. Crowell SP. Louv W. Lemuel M. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the counter antihistamines, ibuprofen and clemastine. *American Journal of Cardiology*. 73(2):346-352, 1994 Feb 15.
- 47 Renwick AG. The metabolism of antihistamines and drug interactions: the role of cytochrome P450 enzymes. *Clinical & Experimental Allergy*. 29 Suppl 3:116-24, 1999 Jul.
- 48 Mason J. Reynolds R. Rao N. The systemic safety of fexofenadine HCl. *Clinical & Experimental Allergy*. 29 Suppl 3:163-70; discussion 171-3, 1999 Jul.

**All References
Screened and Reviewed**

References

- 1 Baelde Y. Dupont P. Cetirizine in children with chronic allergic rhinitis: A multicentre double-blind study of two doses of cetirizine and placebo. *Drug Investigation*. 4(6). 1992. 466-472.
- 2 Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. *Drug Investigation*. 8(4). 1994. 225-233.
- 3 Carlsen KH. Kramer J. Fagertun HE. Larsen S. Loratadine and terfenadine in perennial allergic rhinitis: Treatment of nonresponders to the one drug with the other drug. *Allergy (Copenhagen)*. 48(6). 1993. 431-436.
- 4 A clinical comparison of cetirizine versus astemizole in perennial allergic rhinitis. *Drug Investigation*. 5(4). 1993. 222-228.
- 5 Davies Robert J. Efficacy and tolerability comparison of Ebastine 10 and 20mg with Loratadine 10mg: A double-blind, randomised study in patients with perennial allergic rhinitis. *Clinical Drug Investigation*. 16(6). Dec., 1998. 413-420.
- 6 Fasce Lilla. Ciprandi Giorgio. Pronzato Caterina. Cozzani Simonetta. Grimaldi Maria Angela Vv Toscana. Canonica Giorgio Walter. Cetirizine reduces ICAM-1 on epithelial cells during nasal minimal persistent inflammation in asymptomatic children with mite-allergic asthma. *International Archives of Allergy & Immunology*. 109(3). 1996. 272-276.
- 7 Jacobi Henrik H. Skov Per S. Poulsen Lars K. Malling Hans-Jorgen. Mygind Niels. Histamine and tryptase in nasal lavage fluid after allergen challenge: Effect of 1 week of pretreatment with intranasal azelastine or systemic cetirizine. *Journal of Allergy & Clinical Immunology*. 103(5 PART 1). May, 1999. 768-772.
- 8 Naclerio Robert M. Inhibition of mediator release during the early reaction to antigen. *Journal of Allergy & Clinical Immunology*. 90(4 PART 2). 1992. 715-719.
- 9 Rajaram S. Suthakaran C. Pradhan S C. Majumder N K. Bapna J S. Double blind randomized clinical trial of cetirizine in the treatment of perennial allergic rhinitis. *Indian Journal of Pharmacology*. 26(2). 1994. 112-116.
- 10 Roquet A. Raud J. Hallden G. Van Hage-Hamsten M. Hed J. Hansson L-O. Zetterstrom O. Gronneberg R. Effects of loratadine on anti-IgE-induced inflammation, histamine release, and leukocyte recruitment in skin of atopics. *Allergy (Copenhagen)*. 50(5). 1995. 414-420.
- 11 Sichletidis Lazaros. Dascalopoulou E. Chloros D. Kyriazis G. Kosmidou I. Ioannov J. Seasonal allergic rhinitis, physical exercise and anti-H1 agents. *Acta Therapeutica*. 19(4). 1993. 349-355.
- 12 Tanaka Shigehiro. Hirata Kazuto. Kurihara Naotsugu. Yoshikawa Junichi. Takeda Tadao. Effect of loratadine, an H-1 antihistamine, on induced cough in non-asthmatic patients with chronic cough. *Thorax*. 51(8). 1996. 810-814.
- 13 Tinkelman David G. Kemp James. Mitchell Don Q. Galant Stanley P. Treatment of seasonal allergic rhinitis in children with cetirizine or chlorpheniramine: A multicenter study. *Pediatric Asthma Allergy & Immunology*. 10(1). 1996. 9-17.
- 14 Sedation and performance issues in the treatment of allergic conditions. *Archives of Internal Medicine*. 157(5):494-500, 1997 Mar 10.
- 15 Suppressive effect of loratadine on allergen-induced histamine release in the nose. *Allergy*. 46(7):540-6, 1991 Oct.
- 16 Investigation of the tendency to wheeze in pollen sensitive patients. *Clinical & Experimental Allergy*. 22(10):916-22, 1992 Oct.
- 17 Backhouse CI. Renton R. Fidler C. Rosenberg RM. Multicentre, double-blind comparison of terfenadine and cetirizine in patients with seasonal allergic rhinitis. *British Journal of Clinical Practice*. 44(3):88-91, 1990 Mar.
- 18 Banov CH. Comparative efficacy of once daily loratadine versus terfenadine in the treatment of allergic rhinitis. *Journal of International Medical Research*. 17(2):150-6, 1989 Mar-Apr.
- 19 Barenholtz HA. McLeod DC. Loratadine: a non-sedating antihistamine with once-daily dosing. *DICP*. 23(6):445-50, 1989 Jun.
- 20 Baroody F. Proud D. Kagey-Sobotka A. Freidhoff L. Norman PS. Lichtenstein LM. Naclerio RM. The effects of H1 antihistamines on the early allergic response. *Annals of Allergy*. 63(6 Pt 2):551-5, 1989 Dec.

- 21 Bedard PM, Del Carpio J, Drouin MA, Yang W, Hebert J, Lavoie A, Prevost M, Turenne Y, PetitClerc C, Lorber R. Onset of action of loratadine and placebo and other efficacy variables in patients with seasonal allergic rhinitis. *Clinical Therapeutics*. 14(2):268-75, 1992 Mar-Apr.
- 22 Comparison of the effects of loratadine and astemizole in the treatment of children with seasonal allergic rhinoconjunctivitis. *Allergy*. 47(2 Pt 1):98-102, 1992 Apr.
- 23 Borici-Mazi R, Kouridakis S, Kontou-Fili K. Cutaneous responses to substance P and calcitonin gene-related peptide in chronic urticaria: the effect of cetirizine and dimethindene. *Allergy*. 54(1):46-56, 1999 Jan.
- 24 Bousquet J. Rapid symptom relief in rhinitis. *Clinical & Experimental Allergy*. 29 Suppl 1:25-9, 1999 Mar.
- 25 Bousquet J, Lebel B, Chanal I, Morel A, Michel FB. Antiallergic activity of H1-receptor antagonists assessed by nasal challenge. *Journal of Allergy & Clinical Immunology*. 82(5 Pt 1):881-7, 1988 Nov.
- 26 Braunstein G, Malaquin F, Fajac I, Melac M, Frossard N. Inhibition of histamine-induced nasal obstruction by cetirizine in allergic rhinitis. *British Journal of Clinical Pharmacology*. 33(4):445-8, 1992 Apr.
- 27 Bruttman G, Charpin D, Germouty J, Horak F, Kunkel G, Wittmann G. Evaluation of the efficacy and safety of loratadine in perennial allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 83(2 Pt 1):411-6, 1989 Feb.
- 28 Bruttman G, Pedrali P. Loratadine (SCH29851) 40 mg once daily versus terfenadine 60 mg twice daily in the treatment of seasonal allergic rhinitis. *Journal of International Medical Research*. 15(2):63-70, 1987 Mar-Apr.
- 29 Bryson HM, Faulds D. Intranasal fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in allergic rhinitis. *Drugs*. 43(5):760-75, 1992 May.
- 30 Charlesworth EN, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Effect of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. *Journal of Allergy & Clinical Immunology*. 83(5):905-12, 1989 May.
- 31 Clissold SP, Sorkin EM, Goa KL. Loratadine. A preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. 37(1):42-57, 1989 Jan.
- 32 Davies BH. Prophylactic treatment of seasonal allergic rhinitis. *Clinical Therapeutics*. 13(1):87-91, 1991 Jan-Feb.
- 33 Del Carpio J, Kabbash L, Turenne Y, Prevost M, Hebert J, Bedard PM, Nediiski M, Gutkowski A, Schulz J. Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 84(5 Pt 1):741-6, 1989 Nov.
- 34 Dijkman JH, Hekking PR, Molkenboer JF, Nierop G, Vanderschueren R, Bernheim J, Van Ganse EH. Prophylactic treatment of grass pollen-induced asthma with cetirizine. *Clinical & Experimental Allergy*. 20(5):483-90, 1990 Sep.
- 35 Dockhorn RJ, Bergner A, Connell JT, Falliers CJ, Grabiec SV, Weiler JM, Shellenberger MK. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. *Annals of Allergy*. 58(6):407-11, 1987 Jun.
- 36 Fadel R, David B, Rassemont R, Herpin-Richard N, Borgnon A, Rihoux JP. Eosinophil infiltration: effects of H1 antihistamines. *Journal of the American Academy of Dermatology*. 24(6 Pt 2):1094-6, 1991 Jun.
- 37 Fadel R, Herpin-Richard N, Rihoux JP, Henocq E. Inhibitory effect of cetirizine 2HCl on eosinophil migration in vivo. *Clinical Allergy*. 17(4):373-9, 1987 Jul.
- 38 Falliers CJ, Brandon ML, Buchman E, Connell JT, Dockhorn R, Leese PT, Miller J, Wasserman SI, Zeterberg JM, Altman R, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. *Annals of Allergy*. 66(3):257-62, 1991 Mar.
- 39 Frolund L. Efficacy of an oral antihistamine, loratadine, as compared with a nasal steroid spray, beclomethasone dipropionate, in seasonal allergic rhinitis. *Clinical Otolaryngology & Allied Sciences*. 16(6):527-31, 1991 Dec.
- 40 Frolund L, Etholm B, Irander K, Johannessen TA, Odkvist L, Ohlander B, Weeke B. A multicentre study of loratadine, clemastine and placebo in patients with perennial allergic rhinitis. *Allergy*. 45(4):254-61, 1990 May.
- 41 Golden SJ, Craig TJ. Efficacy and safety of azelastine nasal spray for the treatment of allergic rhinitis. *Journal of the American Osteopathic Association*. 99(7 Suppl):S7-12, 1999 Jul.

- 42 Gutkowski A, Bedard P, Del Carpio J, Hebert J, Prevost M, Schulz J, Turenne Y, Yeadon C. Comparison of the efficacy and safety of loratadine, terfenadine, and placebo in the treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 81(5 Pt 1):902-7, 1988 May.
- 43 Henocq E, Rihoux JP. Does reversed-type anaphylaxis in healthy subjects mimic a real allergic reaction?. *Clinical & Experimental Allergy*. 20(3):269-72, 1990 May.
- 44 Horak F, Bruttman G, Pedrali P, Weeke B, Frolund L, Wolff HH, Christophers E. A multicentric study of loratadine, terfenadine and placebo in patients with seasonal allergic rhinitis. *Arzneimittel-Forschung*. 38(1):124-8, 1988 Jan.
- 45 Irander K, Odkvist LM, Ohlander B. Treatment of hay fever with loratadine—a new non-sedating antihistamine. *Allergy*. 45(2):86-91, 1990 Feb.
- 46 Jeal W, Faulds D. Triamcinolone acetonide. A review of its pharmacological properties and therapeutic efficacy in the management of allergic rhinitis. *Drugs*. 53(2):257-80, 1997 Feb.
- 47 Nonsedating antihistamines: pharmacology, clinical efficacy and adverse effects. *American Family Physician*. 45(3):1337-42, 1992 Mar.
- 48 Katelaris C. Comparative effects of loratadine and azatadine in the treatment of seasonal allergic rhinitis. *Asian Pacific Journal of Allergy & Immunology*. 8(2):103-7, 1990 Dec.
- 49 Klementsson H, Andersson M, Pipkorn U. Allergen-induced increase in nonspecific nasal reactivity is blocked by antihistamines without a clear-cut relationship to eosinophil influx. *Journal of Allergy & Clinical Immunology*. 86(4 Pt 1):466-72, 1990 Oct.
- 50 Lobaton P, Moreno F, Coulie P. Comparison of cetirizine with astemizole in the treatment of perennial allergic rhinitis and study of the concomitant effect on histamine and allergen-induced wheal responses. *Annals of Allergy*. 65(5):401-5, 1990 Nov.
- 51 Mansmann HC Jr, Altman RA, Berman BA, Buchman E, Dockhorn RJ, Leese PT, Love SJ, Middleton E Jr. Efficacy and safety of cetirizine therapy in perennial allergic rhinitis. *Annals of Allergy*. 68(4):348-53, 1992 Apr.
- 52 McNeely W, Wiseman LR. Intranasal azelastine. A review of its efficacy in the management of allergic rhinitis [published erratum appears in *Drugs* 1999 Jan;57(1):8]. *Drugs*. 56(1):91-114, 1998 Jul.
- 53 Michel L, De Vos C, Rihoux JP, Burtin C, Benveniste J, Dubertret L. Inhibitory effect of oral cetirizine on in vivo antigen-induced histamine and PAF-acether release and eosinophil recruitment in human skin. *Journal of Allergy & Clinical Immunology*. 82(1):101-9, 1988 Jul.
- 54 Naclerio RM. Additional properties of cetirizine, a new H1 antagonist. *Allergy Proceedings*. 12(3):187-91, 1991 May-Jun.
- 55 Naclerio RM, Proud D, Kagey-Sobotka A, Freidhoff L, Norman PS, Lichtenstein LM. The effect of cetirizine on early allergic response. *Laryngoscope*. 99(6 Pt 1):596-9, 1989 Jun.
- 56 Noble S, McTavish D. Levocabastine. An update of its pharmacology, clinical efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. *Drugs*. 50(6):1032-49, 1995 Dec.
- 57 Oei HD. Double-blind comparison of loratadine (SCH 29851), astemizole, and placebo in hay fever with special regard to onset of action. *Annals of Allergy*. 61(6):436-9, 1988 Dec.
- 58 Orrust SV, Lamb HM. Mometasone furoate. A review of its intranasal use in allergic rhinitis. *Drugs*. 56(4):725-45, 1998 Oct.
- 59 Panayotopoulos SM, Panayotopoulou ES. Efficacy of cetirizine in the treatment of seasonal allergic rhinoconjunctivitis. *Annals of Allergy*. 65(2):146-8, 1990 Aug.
- 60 Rafferty P. Antihistamines in the treatment of clinical asthma. *Journal of Allergy & Clinical Immunology*. 86(4 Pt 2):647-50, 1990 Oct.
- 61 Redier H, Chanez P, De Vos C, Rifai N, Clauzel AM, Michel FB, Godard P. Inhibitory effect of cetirizine on the bronchial eosinophil recruitment induced by allergen inhalation challenge in allergic patients with asthma. *Journal of Allergy & Clinical Immunology*. 90(2):215-24, 1992 Aug.
- 62 Renton R, Fidler C, Rosenberg R. Multicenter, crossover study of the efficacy and tolerability of terfenadine, 120 mg, versus cetirizine, 10 mg, in perennial allergic rhinitis. *Annals of Allergy*. 67(4):416-20, 1991 Oct.

- 63 Reunala T. Brummer-Korvenkontio H. Petman L. Palosuo T. Sarna S. Effect of ebastine on mosquito bites. *Acta Dermato-Venereologica*. 77(4):315-6, 1997 Jul.
- 64 Reunala T. Lappalainen P. Brummer-Korvenkontio H. Coulie P. Palosuo T. Cutaneous reactivity to mosquito bites: effect of cetirizine and development of anti-mosquito antibodies. *Clinical & Experimental Allergy*. 21(5):617-22, 1991 Sep.
- 65 Rihoux JP. Ghys L. Coulie P. Compared peripheral H1 inhibiting effects of cetirizine 2 HCl and loratadine. *Annals of Allergy*. 65(2):139-42, 1990 Aug.
- 66 Rihoux JP. Ghys L. Muhlethaler K. Wuthrich B. The skin as a target organ for the investigation of antiallergic drugs: comparison between cetirizine and terfenadine. *Dermatology*. 184(2):111-5, 1992.
- 67 Rijntjes E. Ghys L. Rihoux JP. Astemizole and cetirizine in the treatment of seasonal allergic rhinitis: a comparative double-blind, multicentre study. *Journal of International Medical Research*. 18(3):219-24, 1990 May-Jun.
- 68 Rivest J. Despontin K. Ghys L. Rihoux JP. Lachapelle JM. Pharmacological modulation by cetirizine and ebastine of the cutaneous reactivity to histamine. *Dermatologica*. 183(3):208-11, 1991.
- 69 Schoeneich M. Pecoud AR. Effect of cetirizine in a conjunctival provocation test with allergens. *Clinical & Experimental Allergy*. 20(2):171-4, 1990 Mar.
- 70 Shall L. Thompson DA. Barkley AS. Millard LG. Comparative inhibition profiles of three non-sedating antihistamines assessed by an extended Lewis model. *Clinical & Experimental Allergy*. 22(7):711-6, 1992 Jul.
- 71 Simons FE. Recent advances in H1-receptor antagonist treatment. *Journal of Allergy & Clinical Immunology*. 86(6 Pt 2):995-9, 1990 Dec.
- 72 Simons FE. Lukowski JL. Becker AB. Simons KJ. Comparison of the effects of single doses of the new H1-receptor antagonists loratadine and terfenadine versus placebo in children. *Journal of Pediatrics*. 118(2):298-300, 1991 Feb.
- 73 Simons FE. New H1-receptor antagonists: clinical pharmacology. *Clinical & Experimental Allergy*. 20 Suppl 2:19-24, 1990 Aug.
- 74 Skassa-Brociek W. Bousquet J. Montes F. Verdier M. Schwab D. Lherminier M. Michel FB. Double-blind placebo-controlled study of loratadine, mequitazine, and placebo in the symptomatic treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 81(4):725-30, 1988 Apr.
- 75 Small P. Suppression of epicutaneous reactivity by terfenadine and loratadine. *Annals of Allergy*. 68(1):30-4, 1992.
- 76 Snyman JR. Sommers DK. van Wyk M. Gregorowski MD. The influence of betahistine on the dynamics of the cutaneous hypersensitivity reaction in patients with grass pollen allergy. *Immunopharmacology*. 30(1):71-8, 1995 Jun.
- 77 Spaeth J. Klimek L. Mosges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. *Allergy*. 51(12):893-906, 1996 Dec.
- 78 Varney V. Gaga M. Frew AJ. De Vos C. Kay AB. The effect of a single oral dose of prednisolone or cetirizine on inflammatory cells infiltrating allergen-induced cutaneous late-phase reactions in atopic subjects. *Clinical & Experimental Allergy*. 22(1):43-9, 1992 Jan.
- 79 Wang D. Clement P. Smitz J. De Waele M. The activity of recent anti-allergic drugs in the treatment of seasonal allergic rhinitis. *Acta Oto-Rhino-Laryngologica Belgica*. 50(1):25-32, 1996.
- 80 Wasserman SI. Broide DH. Marquardt DL. Cetirizine therapy for seasonal allergic rhinitis: alternative dosage schedules. *Clinical Therapeutics*. 13(6):707-13, 1991 Nov-Dec.
- 81 Watson WT. Simons KJ. Chen XY. Simons FE. Cetirizine: a pharmacokinetic and pharmacodynamic evaluation in children with seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 84(4 Pt 1):457-64, 1989 Oct.
- 82 Wiseman LR. Faulds D. Ebastine. a review of its pharmacological properties and clinical efficacy in the treatment of allergic disorders. *Drugs*. 51(2):260-77, 1996 Feb.
- 83 Wiseman LR. Benfield P. Intranasal fluticasone propionate. A reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. *Drugs*. 53(5):885-907, 1997 May.
- 84 Wood-Baker R. Holgate ST. The comparative actions and adverse effect profile of single doses of H1-receptor antihistamines in the airways and skin of subjects with asthma. *Journal of Allergy & Clinical Immunology*. 91(5):1005-14, 1993 May.

- 85 de Beule R. Vannieuwenhuysse E. Callier J. Verstraete W. Degreef F. Gregoire M. Robience Y. Stevens W. Libert P. Double-blind placebo-controlled clinical evaluation of oxatimide (R 35443). A novel potent anti-allergic drug in the treatment of hay fever. *Acta Allergologica*. 32(4):278-89, 1977 Aug.
- 86 Munch EP. Soborg M. Norreslet TT. Mygind N. A comparative study of dexchlorpheniramine maleate sustained release tablets and budesonide nasal spray in seasonal allergic rhinitis. *Allergy*. 38(7):517-24, 1983 Oct.
- 87 Jobst S. van den Wijngaert W. Schubert A. van de Venne H. Assessment of the efficacy and safety of three dose levels of cetirizine given once daily in children with perennial allergic rhinitis. *Allergy*. 49(8):598-604, 1994 Sep.
- 88 The effect of cetirizine on sulfidoleukotriene production by blood leukocytes in children with allergic rhinitis. *Allergy*. 50(12):964-9, 1995 Dec.
- 89 Horak F. Toth J. Hirschwehr R. Marks B. Stubner UP. Jager S. Berger U. Schleinzer K. Gunczler P. Effect of continuous allergen challenge on clinical symptoms and mediator release in dust-mite-allergic patients. *Allergy*. 53(1):68-72, 1998 Jan.
- 90 Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis. *Allergy*. 44(6):437-41, 1989 Aug.
- 91 Campbell A. Chanal I. Czarlewski W. Michel FB. Bousquet J. Reduction of soluble ICAM-1 levels in nasal secretion by H1-blockers in seasonal allergic rhinitis. *Allergy*. 52(10):1022-5, 1997 Oct.
- 92 Hebert JR. Nolop K. Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy*. 51(8):569-76, 1996 Aug.
- 93 Gehanno P. Desfougeres JL. Fluticasone propionate aqueous nasal spray compared with oral loratadine in patients with seasonal allergic rhinitis. *Allergy*. 52(4):445-50, 1997 Apr.
- 94 In vivo and ex vivo inhibitory effects of loratadine on histamine release in patients with allergic rhinitis. *Allergy*. 53(12):1183-8, 1998 Dec.
- 95 Sabbah A. Hassoun S. Le Sellin J. Andre C. Sicard H. A double-blind, placebo-controlled trial by the sublingual route of immunotherapy with a standardized grass pollen extract. *Allergy*. 49(5):309-13, 1994 May.
- 96 Grant JA. Danielson L. Rihoux JP. DeVos C. A double-blind, single-dose, crossover comparison of cetirizine, ebastine, epinastine, fexofenadine, terfenadine, and loratadine versus placebo: suppression of histamine-induced wheal and flare response for 24 h in healthy male subjects. *Allergy*. 54(7):700-7, 1999 Jul.
- 97 Ciprandi G. Catrullo A. Cerqueti P. Tosca M. Fiorino N. Canonica GW. Loratadine reduces the expression of ICAM-1. *Allergy*. 53(5):545-6, 1998 May.
- 98 Topical levocabastine compared with oral loratadine for the treatment of seasonal allergic rhinoconjunctivitis. Swedish GP Allergy Team. *Allergy*. 49(8):611-5, 1994 Sep.
- 99 Frossard N. Lacroque J. Melac M. Benabdesselam O. Braun JJ. Glasser N. Pauli G. Onset of action in the nasal antihistaminic effect of cetirizine and loratadine in patients with allergic rhinitis. *Allergy*. 52(2):205-9, 1997 Feb.
- 100 Bousquet J. Czarlewski W. Coughard J. Danzig M. Michel FB. Changes in skin-test reactivity do not correlate with clinical efficacy of H1-blockers in seasonal allergic rhinitis. *Allergy*. 53(6):579-85, 1998 Jun.
- 101 Clement P. Roovers MH. Francillon C. Dodion P. Dose-ranging, placebo-controlled study of cetirizine nasal spray in adults with perennial allergic rhinitis. *Allergy*. 49(8):668-72, 1994 Sep.
- 102 Casale TB. Andrade C. Qu R. Safety and efficacy of once-daily fexofenadine HCl in the treatment of autumn seasonal allergic rhinitis. *Allergy & Asthma Proceedings*. 20(3):193-8, 1999 May-Jun.
- 103 Bronsky EA. Falliers CJ. Kaiser HB. Ahlbrandt R. Mason JM. Effectiveness and safety of fexofenadine, a new non-sedating H1-receptor antagonist, in the treatment of fall allergies. *Allergy & Asthma Proceedings*. 19(3):135-41, 1998 May-Jun.
- 104 The effect of chlorpheniramine on asthma. *Allergy Proceedings*. 11(5):229-33, 1990 Sep-Oct.
- 105 McLoughlin JA. Nall M. Berla E. Effect of allergy medication on children's reading comprehension. *Allergy Proceedings*. 11(5):225-8, 1990 Sep-Oct.

- 106 Pratt CM. Mason J. Russell T. Reynolds R. Ahlbrandt R. Cardiovascular safety of fexofenadine HCl. *American Journal of Cardiology*. 83(10):1451-4, 1999 May 15.
- 107 Wilson WR. Moss J. Joseph M. Laird N. Glinski M. Efficacy of an H1 antagonist, astemizole, for chronic allergic rhinitis. *American Journal of Otolaryngology*. 8(3):157-60, 1987 May-Jun.
- 108 Sierra-Monge JJ. Gazca-Aguilar A. Del Rio-Navarro B. Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis. *American Journal of Therapeutics*. 6(3):149-55, 1999 May.
- 109 Frossard N. Benabdesselam O. Melac M. Glasser N. Lacroque J. Pauli G. Nasal effect of cetirizine and loratadine at 24 hours in patients with allergic rhinitis. *American Journal of Therapeutics*. 5(5):307-11, 1998 Sep.
- 110 Galant S. Zippin C. Bullock J. Crisp J. Allergy skin test. I. Antihistamine inhibition. *Annals of Allergy*. 30(2):53-63, 1972 Feb.
- 111 Brandon ML. Weiner M. Clinical investigation of terfenadine, a non-sedating antihistamine. *Annals of Allergy*. 44(2):71-5, 1980 Feb.
- 112 Lockey RF. Findley S. Mitchell DQ. Woehler T. Lieberman P. Nicodemus CF. Effects of cetirizine versus terfenadine in seasonal allergic rhinitis. *Annals of Allergy*. 70(4):311-5, 1993 Apr.
- 113 Dolovich J. Moote DW. Mazza JA. Clermont A. PetitClerc C. Danzig M. Efficacy of loratadine versus placebo in the prophylactic treatment of seasonal allergic rhinitis. *Annals of Allergy*. 73(3):235-9, 1994 Sep.
- 114 Hyde JS. Floro LD. Theophylline and chlorpheniramine in childhood asthma. Dose requirements for children 6 to 12 years (therapeutic orphans) and young adults 13 to 18 years of age receiving cromolyn sodium prophylaxis. *Annals of Allergy*. 32(2):73-9, 1974 Feb.
- 115 Vuurman EF. van Veggel LM. Uiterwijk MM. Leutner D. O'Hanlon JF. Seasonal allergic rhinitis and antihistamine effects on children's learning. *Annals of Allergy*. 71(2):121-6, 1993 Aug.
- 116 An investigation of the possible disadvantages of antihistamines in allergic asthma. *Annals of Allergy*. 30(2):95-7, 1972 Feb.
- 117 Double-blind, controlled study of clemastine fumarate, chlorpheniramine and placebo in the symptomatic treatment of seasonal allergic rhinitis in desensitized and nondesensitized patients. *Annals of Allergy*. 38(3):175-81, 1977 Mar.
- 118 Chervinsky P. Georgitis J. Banov C. Boggs P. Vande Souwe R. Greenstein S. Once daily loratadine versus astemizole once daily. *Annals of Allergy*. 73(2):109-13, 1994 Aug.
- 119 Double-blind, controlled study of clemastine fumarate, chlorpheniramine and placebo in patients with seasonal allergic rhinitis. *Annals of Allergy*. 38(3):169-74, 1977 Mar.
- 120 Comparison of efficacy and safety of cetirizine and ebastine in patients with perennial allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 80(5):399-403, 1998 May.
- 121 Ciprandi G. Buscaglia S. Catrullo A. Marchesi E. Bianchi B. Canonica GW. Loratadine in the treatment of cough associated with allergic rhinoconjunctivitis. *Annals of Allergy, Asthma, & Immunology*. 75(2):115-20, 1995 Aug.
- 122 Day JH. Briscoe MP. Clark RH. Ellis AK. Gervais P. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 79(2):163-72, 1997 Aug.
- 123 Drouin M. Yang WH. Bertrand B. Van Cauwenberge P. Clement P. Dalby K. Damell R. Ernst TM. Hebert J. Karlsson G. Luciuk G. Mazza J. Roovers M. Ruoppi P. Seppey M. Stem M. Suonpaa J. Sussman G. Tan KY. Tse K. Widjaja P. Jensen P. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. *Annals of Allergy, Asthma, & Immunology*. 77(2):153-60, 1996 Aug.
- 124 Bernstein DI. Schoenwetter WF. Nathan RA. Storms W. Ahlbrandt R. Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 79(5):443-8, 1997 Nov.
- 125 Meltzer EO. Casale TB. Nathan RA. Thompson AK. Once-daily fexofenadine HCl improves quality of life and reduces work and activity impairment in patients with seasonal allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 83(4):311-7, 1999 Oct.
- 126 Kelso JM. Study protocol on azelastine. *Annals of Allergy, Asthma, & Immunology*. 78(2):244, 1997 Feb.

- 127 Berkowitz RB. Dockhorn R. Lockey R. Findlay S. Howland WC. Mitchell DQ. Woehler T. Comparison of efficacy, safety, and skin test inhibition of cetirizine and astemizole. *Annals of Allergy, Asthma, & Immunology*. 76(4):363-8, 1996 Apr.
- 128 Gehanno P. Bremard-Oury C. Zeisser P. Comparison of ebastine to cetirizine in seasonal allergic rhinitis in adults. *Annals of Allergy, Asthma, & Immunology*. 76(6):507-12, 1996 Jun.
- 129 Ciprandi G. Passalacqua G. Mincarini M. Ricca V. Canonica GW. Continuous versus on demand treatment with cetirizine for allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 79(6):507-11, 1997 Dec.
- 130 Sabbah A. Daele J. Wade AG. Ben-Soussen P. Attali P. Comparison of the efficacy, safety, and onset of action of mizolastine, cetirizine, and placebo in the management of seasonal allergic rhinoconjunctivitis. MIZOCET Study Group. *Annals of Allergy, Asthma, & Immunology*. 83(4):319-25, 1999 Oct.
- 131 Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Annals of Allergy, Asthma, & Immunology*. 76(5):440-6, 1996 May.
- 132 Day JH. Briscoe MP. Welsh A. Smith JN. Clark A. Ellis AK. Mason J. Onset of action, efficacy, and safety of a single dose of fexofenadine hydrochloride for ragweed allergy using an environmental exposure unit. *Annals of Allergy, Asthma, & Immunology*. 79(6):533-40, 1997 Dec.
- 133 Lockey RF. Widlitz MD. Mitchell DQ. Lumry W. Dockhorn R. Woehler T. Grossman J. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 76(5):448-54, 1996 May.
- 134 Weiler JM. Bloomfield JR. Woodworth GG. Grant AR. Layton TA. Brown TL. McKenzie DR. Baker TW. Watson GS. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. *Annals of Internal Medicine*. 132(5):354-63, 2000 Mar 7.
- 135 Barnes CL. McKenzie CA. Webster KD. Poinsett-Holmes K. Cetirizine: a new, nonsedating antihistamine. *Annals of Pharmacotherapy*. 27(4):464-70, 1993 Apr.
- 136 Baroody FM. Lim MC. Proud D. Kagey-Sobotka A. Lichtenstein LM. Naclerio RM. Effects of loratadine and terfenadine on the induced nasal allergic reaction. *Archives of Otolaryngology - Head & Neck Surgery*. 122(3):309-16, 1996 Mar.
- 137 Horak F. Jager S. Toth J. Berger U. Efficacy and tolerability of astemizole-D and Loratadine-D during prolonged, controlled allergen challenge in the Vienna Challenge Chamber. *Arzneimittel-Forschung*. 46(11):1077-81, 1996 Nov.
- 138 Olsen OT. Nuchel Petersen L. Hoi L. Lorentzen KA. Hindberg Rasmussen W. Svendsen UG. Comparison of loratadine and terfenadine in allergic seasonal rhinoconjunctivitis with emphasis on nasal stuffiness and peak flow. *Arzneimittel-Forschung*. 42(10):1227-31, 1992 Oct.
- 139 Melillo G. D'Amato G. Zanussi C. Ortolani C. Pastorello E. Loy M. Di Tucci A. Locci F. Del Giacco GS. Lenzi L. Sestini P. Rottoli P. A multicentre controlled trial of terfenadine, dexchlorpheniramine, and placebo in allergic rhinitis. *Arzneimittel-Forschung*. 32(9a):1202-3, 1982.
- 140 Hansen GR. Loratadine in the high performance aerospace environment. *Aviation Space & Environmental Medicine*. 70(9):919-24, 1999 Sep.
- 141 Phillips MJ. Meyrick Thomas RH. Moodley I. Davies RJ. A comparison of the in vivo effects of ketotifen, clemastine, chlorpheniramine and sodium cromoglycate on histamine and allergen induced weals in human skin. *British Journal of Clinical Pharmacology*. 15(3):277-86, 1983 Mar.
- 142 Rosenzweig P. Caplain H. Chaufour S. Ulliac N. Cabanis MJ. Thebault JJ. Comparative wheal and flare study of mizolastine vs terfenadine, cetirizine, loratadine and placebo in healthy volunteers. *British Journal of Clinical Pharmacology*. 40(5):459-65, 1995 Nov.
- 143 The efficacy and sedative profile of astemizole and cetirizine in the treatment of grass pollen hayfever in general practice. *British Journal of Clinical Practice*. 47(3):131-5, 1993 May-Jun.
- 144 Backhouse CI. Rosenberg R. Prophylaxis of whole season hay fever symptomatology: a comparison of terfenadine with chlorpheniramine. *British Journal of Clinical Practice*. 41(11):995-9, 1987 Nov.
- 145 Langrick AF. Wallace MG. A new approach to the treatment of seasonal allergic rhinitis. *British Journal of Clinical Practice*. 36(9):312-4, 1982 Sep.

- 146 Gomez J. Gomez G. Hay fever and allergy in general practice: two antihistamine drugs compared. *British Journal of Clinical Practice*. 21(8):401-3, 1967 Aug.
- 147 Kirkegaard J. Secher C. Borum P. Mygind N. Inhibition of histamine-induced nasal symptoms by the H1 antihistamine chlorpheniramine maleate: demonstration of topical effect. *British Journal of Diseases of the Chest*. 77(2):113-22, 1983 Apr.
- 148 Tkachyk SJ. New treatments for allergic rhinitis. *Canadian Family Physician*. 45:1255-60, 1999 May.
- 149 Braunstein G. Buvry A. Lacroque J. Desjardins N. Frossard N. Do nasal mast cells release histamine on stimulation with substance P in allergic rhinitis? *Clinical & Experimental Allergy*. 24(10):922-9, 1994 Oct.
- 150 Pratt C. Brown AM. Rampe D. Mason J. Russell T. Reynolds R. Ahlbrandt R. Cardiovascular safety of fexofenadine HCl. *Clinical & Experimental Allergy*. 29 Suppl 3:212-6, 1999 Jul.
- 151 Taborda-Barata L. Jacobson M. Walker S. Njuki F. Ying S. Randev P. Durham SR. Kay AB. Effect of cetirizine and prednisolone on cellular infiltration and cytokine mRNA expression during allergen-induced late cutaneous responses. *Clinical & Experimental Allergy*. 26(1):68-78, 1996 Jan.
- 152 Topical levocabastine—an effective alternative to oral antihistamines in seasonal allergic rhinoconjunctivitis. *Clinical & Experimental Allergy*. 25(3):220-7, 1995 Mar.
- 153 Ciprandi G. Pronzato C. Ricca V. Passalacqua G. Danzig M. Canonica GW. Loratadine treatment of rhinitis due to pollen allergy reduces epithelial ICAM-1 expression. *Clinical & Experimental Allergy*. 27(10):1175-83, 1997 Oct.
- 154 Bentley AM. Walker S. Hanotte F. De Vos C. Durham SR. A comparison of the effects of oral cetirizine and inhaled beclomethasone on early and late asthmatic responses to allergen and the associated increase in airways hyperresponsiveness. *Clinical & Experimental Allergy*. 26(8):909-17, 1996 Aug.
- 155 Ciprandi G. Tosca M. Ricca V. Passalacqua G. Riccio AM. Bagnasco M. Canonica GW. Cetirizine treatment of rhinitis in children with pollen allergy: evidence of its antiallergic activity. *Clinical & Experimental Allergy*. 27(10):1160-6, 1997 Oct.
- 156 Juniper EF. Cartier A. Trebilcock AL. Frith PA. Dolovich J. Hargreave FE. Effects of oxafomide compared with chlorpheniramine in allergic rhinoconjunctivitis. *Clinical Allergy*. 11(1):61-6, 1981 Jan.
- 157 Taylor G. Shivalkar PR. Local nasal desensitization in allergic rhinitis. *Clinical Allergy*. 2(2):125-36, 1972 Jun.
- 158 Pearman DS. Lumry WR. Winder JA. Noonan MJ. Once-daily cetirizine effective in the treatment of seasonal allergic rhinitis in children aged 6 to 11 years: a randomized, double-blind, placebo-controlled study. *Clinical Pediatrics*. 36(4):209-15, 1997 Apr.
- 159 The role of histamine receptors in asthma. *Clinical Science*. 60(4):363-70, 1981 Apr.
- 160 Lutsky BN. Klose P. Melon J. Menardo JL. Molkhou P. Ronchetti R. Suonpaa J. Wahn U. Wessel F. A comparative study of the efficacy and safety of loratadine syrup and terfenadine suspension in the treatment of 3- to 6-year-old children with seasonal allergic rhinitis. *Clinical Therapeutics*. 15(5):855-65, 1993 Sep-Oct.
- 161 Ricard N. Kind P. Christian S. Jensen M. Stewart J. Link between patient preferences and treatment outcomes in seasonal allergic rhinitis: an empiric investigation. *Clinical Therapeutics*. 21(1):268-77, 1999 Jan.
- 162 Schoenwetter W. Lim J. Comparison of intranasal triamcinolone acetonide with oral loratadine for the treatment of patients with seasonal allergic rhinitis. *Clinical Therapeutics*. 17(3):479-92, 1995 May-Jun.
- 163 Scott DW. Miller WH Jr. Nonsteroidal management of canine pruritus: chlorpheniramine and a fatty acid supplement (DVM Derm Caps) in combination, and the fatty acid supplement at twice the manufacturer's recommended dosage. *Cornell Veterinarian*. 80(4):381-7, 1990 Oct.
- 164 Muler H. Blum F. Double-blind comparison of two antihistamines: mequitazine and dexchlorpheniramine. *Current Medical Research & Opinion*. 5(5):359-65, 1978.
- 165 Todd G. Hopkins P. MacLay WP. Double-blind trials of clemastine ('Tavegil') in allergic rhinitis. *Current Medical Research & Opinion*. 3(3):126-31, 1975.

- 166 Sheriff JM. Wallace MG. A comparative study of clemastine ("Tavegil") and chlorpheniramine maleate in the treatment of hay fever. *Current Medical Research & Opinion*. 4(4):245-9, 1976.
- 167 Meltzer EO. The use of antihistamines for the treatment of airway disease. *Cutis*. 42(4A):22-5, 1988 Oct 27.
- 168 Shanon A. Feldman W. Leikin L. Pong AH. Peterson R. Williams V. Comparison of CNS adverse effects between astemizole and chlorpheniramine in children: a randomized, double-blind study. *Developmental Pharmacology & Therapeutics*. 20(3-4):239-46, 1993.
- 169 Spencer CM. Faulds D. Peters DH. Cetirizine. A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs*. 46(6):1055-80, 1993 Dec.
- 170 Markham A. Wagstaff AJ. Fexofenadine. *Drugs*. 55(2):269-74; discussion 275-6, 1998 Feb.
- 171 Slater JW. Zechin AD. Haxby DG. Second-generation antihistamines: a comparative review. *Drugs*. 57(1):31-47, 1999 Jan.
- 172 Hana M. Fitton A. Peters DH. Loratadine. A reappraisal of its pharmacological properties and therapeutic use in allergic disorders. *Drugs*. 48(4):617-37, 1994 Oct.
- 173 Cohen B. Gehanno P. Comparison of the efficacy of ebastine 10mg and 20mg once daily with that of cetirizine 10mg once daily in adults with seasonal allergic rhinitis. A multicentre double-blind study. *Drugs*. 52 Suppl 1:26-9, 1996.
- 174 Simpson K. Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs*. 59(2):301-21, 2000 Feb.
- 175 Charpin D. Godard P. Garay RP. Baehre M. Herman D. Michel FB. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. *European Archives of Oto-Rhino-Laryngology*. 252(8):455-8, 1995.
- 176 Stone BM. Turner C. Mills SL. Nicholson AN. Studies into the possible central effects of the H-1 receptor antagonist, fexofenadine. *International Archives of Allergy & Immunology*. 118(2-4):338, 1999 Feb-Apr.
- 177 Lippert U. Hoer A. Moller A. Ramboer I. Cremer B. Henz BM. Role of antigen-induced cytokine release in atopic pruritus. *International Archives of Allergy & Immunology*. 116(1):36-9, 1998 May.
- 178 Clinical pharmacology of tritoequaline: a comparative study against dexchlorpheniramine in allergic rhinitis. *International Journal of Clinical Pharmacology Research*. 6(2):113-8, 1986.
- 179 Taylor RJ. Long WF. Nelson HS. The development of subsensitivity to chlorpheniramine. *Journal of Allergy & Clinical Immunology*. 76(1):103-7, 1985 Jul.
- 180 Effect of cetirizine, a new H1 antihistamine, on the early and late allergic reactions in a bronchial provocation test with allergen. *Journal of Allergy & Clinical Immunology*. 91(6):1189-97, 1993 Jun.
- 181 Bousquet J. Duchateau J. Pignat JC. Fayol C. Marquis P. Mariz S. Ware JE. Valentin B. Burtin B. Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French version of the SF-36 questionnaire. *Journal of Allergy & Clinical Immunology*. 98(2):309-16, 1996 Aug.
- 182 Burns M. Shanaman JE. Shellenberger CH. A laboratory study of patients with chronic allergic rhinitis: antihistamine effects on skilled performance. *Journal of Allergy & Clinical Immunology*. 93(4):716-24, 1994 Apr.
- 183 Zweiman B. Atkins PC. Moskovitz A. von Allmen C. Ciliberti M. Grossman S. Cellular inflammatory responses during immediate, developing, and established late-phase allergic cutaneous reactions: effects of cetirizine. *Journal of Allergy & Clinical Immunology*. 100(3):341-7, 1997 Sep.
- 184 Hartley TF. Lieberman PL. Meltzer EO. Noyes JN. Pearlman DS. Tinkelman DG. Efficacy and tolerance of flucocortin butyl administered twice daily in adult patients with perennial rhinitis. *Journal of Allergy & Clinical Immunology*. 75(4):501-7, 1985 Apr.
- 185 Jordana G. Dolovich J. Briscoe MP. Day JH. Drouin MA. Gold M. Robson R. Stepler N. Yang W. Intranasal fluticasone propionate versus loratadine in the treatment of adolescent patients with seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 97(2):588-95, 1996 Feb.
- 186 Nathan RA. Segall N. Schocket AL. A comparison of the actions of H1 and H2 antihistamines on histamine-induced bronchoconstriction and cutaneous wheal response in asthmatic patients. *Journal of Allergy & Clinical Immunology*. 67(3):171-7, 1981 Mar.

- 187 Ciprandi G. Buscaglia S. Pesce G. Passalacqua G. Rihoux JP. Bagnasco M. Canonica GW. Cetirizine reduces inflammatory cell recruitment and ICAM-1 (or CD54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge. *Journal of Allergy & Clinical Immunology*. 95(2):612-21, 1995 Feb.
- 188 Harvey RP. Comer C. Sanders B. Westley R. Marsh W. Shapiro H. Wiener M. Model for outcomes assessment of antihistamine use for seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 97(6):1233-41, 1996 Jun.
- 189 Day JH. Briscoe M. Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *Journal of Allergy & Clinical Immunology*. 101(5):638-45, 1998 May.
- 190 Weiler JM. Donnelly A. Campbell BH. Connell JT. Diamond L. Hamilton LH. Rosenthal RR. Hemsworth GR. Perhach JL Jr. Multicenter, double-blind, multiple-dose, parallel-groups efficacy and safety trial of azelastine, chlorpheniramine, and placebo in the treatment of spring allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 82(5 Pt 1):801-11, 1988 Nov.
- 191 Cohan RH. Bloom FL. Rhoades RB. Wittig HJ. Haugh LD. Treatment of perennial allergic rhinitis with cromolyn sodium. Double-blind study on 34 adult patients. *Journal of Allergy & Clinical Immunology*. 58(1 PT. 2):121-8, 1976 Jul.
- 192 Parsi L. Demoly P. Harris AG. Tisserand B. Michel FB. Bousquet J. Comparison between nasal provocation tests and skin tests in patients treated with loratadine and cetirizine. *Journal of Allergy & Clinical Immunology*. 103(4):591-4, 1999 Apr.
- 193 Wong L. Hendeles L. Weinberger M. Pharmacologic prophylaxis of allergic rhinitis: relative efficacy of hydroxyzine and chlorpheniramine. *Journal of Allergy & Clinical Immunology*. 67(3):223-8, 1981 Mar.
- 194 Weiler JM. Meltzer EO. Benson PM. Weiler K. Widlitz MD. Freitag J. A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model. *Journal of Allergy & Clinical Immunology*. 94(6 Pt 1):972-80, 1994 Dec.
- 195 Prenner BM. Chervinsky P. Hampel FC Jr. Howland WC. Lawrence M. Meltzer EO. Munk ZM. Ratner PH. Seltzer JM. Settiani GA. Lorber RR. Harrison JE. Double-strength beclomethasone dipropionate (84 micrograms/spray) aqueous nasal spray in the treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 98(2):302-8, 1996 Aug.
- 196 Grant JA. Nicodemus CF. Findlay SR. Glovsky MM. Grossman J. Kaiser H. Meltzer EO. Mitchell DQ. Pearlman D. Selner J. et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *Journal of Allergy & Clinical Immunology*. 95(5 Pt 1):923-32, 1995 May.
- 197 Multi-center, double-blind, placebo-controlled trial of flucortin butyl in perennial rhinitis. *Journal of Allergy & Clinical Immunology*. 71(6):597-603, 1983 Jun.
- 198 Carpenter GB. Bunker-Soler AL. Nelson HS. Evaluation of combined H1- and H2-receptor blocking agents in the treatment of seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 71(4):412-7, 1983 Apr.
- 199 Greiff L. Persson CG. Svensson C. Enander I. Andersson M. Loratadine reduces allergen-induced mucosal output of alpha 2-macroglobulin and tryptase in allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 96(1):97-103, 1995 Jul.
- 200 Meltzer EO. Weiler JM. Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology*. 97(2):617-26, 1996 Feb.
- 201 Nielsen L. Johnsen CR. Mosbech H. Poulsen LK. Malling HJ. Antihistamine premedication in specific cluster immunotherapy: a double-blind, placebo-controlled study. *Journal of Allergy & Clinical Immunology*. 97(6):1207-13, 1996 Jun.
- 202 Howarth PH. Stern MA. Roi L. Reynolds R. Bousquet J. 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. *Journal of Allergy & Clinical Immunology*. 104(5):927-33, 1999 Nov.
- 203 Perennial allergic rhinitis: clinical efficacy of a new antihistamine. *Journal of Allergy & Clinical Immunology*. 86(6 Pt 2):1004-8, 1990 Dec.
- 204 Terrien MH. Rahm F. Fellrath JM. Spertini F. Comparison of the effects of terfenadine with fexofenadine on nasal provocation tests with allergen. *Journal of Allergy & Clinical Immunology*. 103(6):1025-30, 1999 Jun.

- 205 Vermeeren A. O'Hanlon JF. Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance. *Journal of Allergy & Clinical Immunology*. 101(3):306-11, 1998 Mar.
- 206 Baroody FM. Gungor A. deTineo M. Haney L. Blair C. Naclerio RM. Comparison of the response to histamine challenge of the nose and the maxillary sinus: effect of loratadine. *Journal of Applied Physiology*. 87(3):1038-47, 1999 Sep.
- 207 Druce HM. Thoden WR. Mure P. Furey SA. Lockhart EA. Xie T. Galant S. Prenner BM. Weinstein S. Ziering R. Brandon ML. Brompheniramine, loratadine, and placebo in allergic rhinitis: a placebo-controlled comparative clinical trial. *Journal of Clinical Pharmacology*. 38(4):382-9, 1998 Apr.
- 208 Gutkowski A. Del Carpio J. Gelinas B. Schulz J. Turenne Y. Comparative study of the efficacy, tolerance and side-effects of dexchlorpheniramine maleate 6 mg b.i.d. with terfenadine 60 mg b.i.d. *Journal of International Medical Research*. 13(5):284-8, 1985.
- 209 Passali D. Piragine F. A comparison of azelastine nasal spray and cetirizine tablets in the treatment of allergic rhinitis. *Journal of International Medical Research*. 22(1):17-23, 1994 Jan-Feb.
- 210 Bhatt AD. Vaidya AB. Sane SP. Sahani S. Koya R. Rajaseharan A. Perumal SV. Chauhan CK. Pathak KJ. Sainath BR. et al. Comparative effect of dimethindene maleate and chlorpheniramine maleate on histamine-induced weal and flare. *Journal of International Medical Research*. 19(6):479-83, 1991 Nov-Dec.
- 211 Bentley S. Performance in students with seasonal allergy. *Journal of International Medical Research*. 8(3):221-3,
- 212 Kagan G. Dabrowicki E. Huddleston L. Kapur TR. Wolstencroft P. A double blind trial of terfenadine and placebo in hay fever using a substitution technique for non-responders. *Journal of International Medical Research*. 8(6):404-7, 1980.
- 213 Gambardella R. A comparison of the efficacy of azelastine nasal spray and loratadine tablets in the treatment of seasonal allergic rhinitis. *Journal of International Medical Research*. 21(5):268-75, 1993 Sep-Oct.
- 214 Horak F. Jager S. Berger U. Onset and duration of the effects of three antihistamines in current use—astemizole, loratadine and terfenadine forte—studied during prolonged, controlled allergen challenges in volunteers. *Journal of International Medical Research*. 20(5):422-34, 1992 Sep.
- 215 A parallel-group comparison of astemizole and loratadine for the treatment of perennial allergic rhinitis. *Journal of International Medical Research*. 25(4):175-81, 1997 Jul-Aug.
- 216 Ciprandi G. Iudice A. Tosca MA. Ruffoni S. Buscaglia S. Canonica GW. Comparative effects of terfenadine and loratadine in the treatment of hay fever. *Journal of Investigational Allergology & Clinical Immunology*. 1(6):368-72, 1991 Dec.
- 217 Chyrek-Borowska S. Siergiejko Z. Michalska I. The effects of a new generation of H1 antihistamines (cetirizine and loratadine) on histamine release and the bronchial response to histamine in atopic patients. *Journal of Investigational Allergology & Clinical Immunology*. 5(2):103-7, 1995 Mar-Apr.
- 218 Raptopoulou-Gigi M. Ilonidis G. Orphanou-Koumerkeridou H. Preponis C. Sidiropoulos J. Lazaridis T. Goulis G. The effect of loratadine on activated cells of the nasal mucosa in patients with allergic rhinitis. *Journal of Investigational Allergology & Clinical Immunology*. 3(4):192-7, 1993 Jul-Aug.
- 219 Comparative study of terfenadine and cetirizine in hay fever: assessment of efficacy and central nervous system effects. *Journal of Investigational Allergology & Clinical Immunology*. 5(1):40-6, 1995 Jan-Feb.
- 220 Multicenter double-blind comparative study of terfenadine and cetirizine in hay fever. *Journal of Investigational Allergology & Clinical Immunology*. 2(3):162-6, 1992 May-Jun.
- 221 Ballmer-Weber BK. Gex-Collet C. Wuthrich B. Inhibition of histamine or allergen-induced wheals by a single dose of acrivastine, fexofenadine or cetirizine. *Journal of Investigational Allergology & Clinical Immunology*. 9(6):351-5, 1999 Nov-Dec.
- 222 Lewiston NJ. Johnson S. Sloan E. Effect of antihistamine on pulmonary function of children with asthma. *Journal of Pediatrics*. 101(3):458-60, 1982 Sep.
- 223 Simons FE. Reggin JD. Roberts JR. Simons KJ. Benefit/risk ratio of the antihistamines (H1-receptor antagonists) terfenadine and chlorpheniramine in children. *Journal of Pediatrics*. 124(6):979-83, 1994 Jun.

- 224 Gupta SK. Reversion and antihistamines. *Journal of the Association of Physicians of India*. 44(1):72-3, 1996 Jan.
- 225 van der Bijl WJ, Cordier R, van Dishoeck EA, De Proost W, Vannieuwenhuysse E. A double-blind comparison of oxatomide (R 35 443) and diphenhydramine in the treatment of hay fever. *Laryngoscope*. 90(1):145-51, 1980 Jan.
- 226 Miller J. A double-blind study of d-isoephedrine combined with chlorpheniramine in symptomatic relief of hay fever. *Medical Times*. 95(3):306-9, 1967 Mar.
- 227 Buckley CE 3d, Klemawesch SJ, Lucas SK. Treatment of allergic rhinitis with a new selective H1 antihistamine: terfenadine. *New England & Regional Allergy Proceedings*. 6(1):63-70, 1985 Winter.
- 228 Crawford WW, Klaustermeyer WB, Lee PH, Placik IM. Comparative efficacy of terfenadine, loratadine, and astemizole in perennial allergic rhinitis. *Otolaryngology - Head & Neck Surgery*. 118(5):668-73, 1998 May.
- 229 Naclerio RM. The effect of antihistamines on the immediate allergic response: a comparative review. *Otolaryngology - Head & Neck Surgery*. 108(6):723-30, 1993 Jun.
- 230 Masi M, Candiani R, van de Venne H. A placebo-controlled trial of cetirizine in seasonal allergic rhino-conjunctivitis in children aged 6 to 12 years. *Pediatric Allergy & Immunology*. 4(4 Suppl):47-52, 1993.
- 231 Cetirizine for seasonal allergic rhinitis in children aged 2-6 years. A double-blind comparison with placebo. *Pediatric Allergy & Immunology*. 4(3):157-61, 1993 Aug.
- 232 Simons FE, Fraser TG, Reggin JD, Roberts JR, Simons KJ. Adverse central nervous system effects of older antihistamines in children. *Pediatric Allergy & Immunology*. 7(1):22-7, 1996 Feb.
- 233 Connell JT. Pharmacology and clinical efficacy of terfenadine, a new H1-receptor antagonist. *Pharmacotherapy*. 5(4):201-8, 1985 Jul-Aug.
- 234 Pastorello EA, Ortolani C, Gerosa S, Praveltoni V, Codecasa LR, Fugazza A, Zanussi C. Antihistaminic treatment of allergic rhinitis: a double-blind study with terfenadine versus dexchlorpheniramine. *Pharmatherapeutica*. 5(2):69-75, 1987.
- 235 Brostoff J, Lockhart JD. Controlled trial of terfenadine and chlorpheniramine maleate in perennial rhinitis. *Postgraduate Medical Journal*. 58(681):422-3, 1982 Jul.
- 236 Backhouse CI, Brewster BS, Lockhart JD, Maneksha S, Purvis CR, Valle-Jones JC. Terfenadine in allergic rhinitis. A comparative trial of a new antihistamine versus chlorpheniramine and placebo. *Practitioner*. 226(1364):347-51, 1982 Feb.
- 237 Wheatley D. Ketotifen in hay fever and allergic rhinitis. *Practitioner*. 228(1393):685-6, 1984 Jul.
- 238 Pukander JS, Karma PH, Penttila MA, Perala ME, Ylitalo P, Kataja MJ. Mequitazine and dexchlorpheniramine in perennial rhinitis. A double-blind cross-over placebo-controlled study. *Rhinology*. 28(4):249-56, 1990 Dec.
- 239 Comparison of mizolastine with loratadine in the treatment of perennial allergic rhinitis. *Rhinology*. 34(2):101-4, 1996 Jun.
- 240 Johansen LV, Bjerrum P, Illium P. Treatment of seasonal allergic rhinitis—a double blind, group comparative study of terfenadine and dexchlorpheniramine. *Rhinology*. 25(1):35-40, 1987 Mar.
- 241 Wood SF. Clinical experience with non-sedating antihistamines in paediatric allergic rhinitis. *Rhinology - Supplement*. 13:27-37, 1992 Sep.
- 242 Lee ST, Amin MJ. Efficacy and safety of loratadine compared with astemizole in Malaysian patients with allergic rhinitis. *Singapore Medical Journal*. 35(6):591-4, 1994 Dec.
- 243 Heron TG. Double-blind cross-over study of Demazin Chronosules capsules and Eskomade spansules. *South African Medical Journal*. 46(19):579-81, 1972 May 6.
- 244 Bronsky EA, Falliers CJ, Kaiser HB, et al. Effectiveness and safety of fexofenadine, a new non-sedating H1-receptor antagonist, in the treatment of Fall allergies. *Allergy Asthma Proc*. 1998 May-June; 19:135-41.
- 245 Sussman GL, Mason J, Compton D, Stewart J, Ricard N. The efficacy and safety of fexofenadine HCl and pseudoephedrine, alone and in combination, in seasonal allergic rhinitis. *J. Allergy Clin Immunol* 1999;104:100-6
- 246 Davies BH. Prophylactic Treatment of Seasonal Allergic Rhinitis *Clinical Therapeutics* 1991;13:87-91

- 247 Tagliatalata M. Timmerman H. Annunziato L. Cardiotoxic potential and CNS effects of first-generation antihistamines. *Trends in Pharmacological Sciences*. 21(2):52-6, 2000 Feb.
- 248 Delgado LF. Piferferman A. Sole D. Nasplitz CK. Evaluation of the potential cardiotoxicity of the antihistamines terfenadine, astemizole, loratadine, and cetirizine in atopic children. *Annals of Allergy, Asthma, & Immunology*. 80(4):333-7, 1998 Apr.
- 249 Nicholson AN. Stone BM. Turner C. Mills SL. Antihistamines and aircrew: usefulness of fexofenadine. *Aviation Space & Environmental Medicine*. 71(1):2-6, 2000 Jan.
- 250 Gonzalez MA. Estes KS. Pharmacokinetic overview of oral second-generation H1 antihistamines. *International Journal of Clinical Pharmacology & Therapeutics*. 36(5):292-300, 1998 May.
- 251 Rihoux JP. Therapeutic index of H1-antihistamines: example of cetirizine. *Annals of Allergy, Asthma, & Immunology*. 83(5):489-92, 1999 Nov.
- 252 Estelle F. Simons R. H1-receptor antagonists: safety issues. *Annals of Allergy, Asthma, & Immunology*. 83(5):481-8, 1999 Nov.
- 253 Impact of cetirizine on the burden of allergic rhinitis. *Annals of Allergy, Asthma, & Immunology*. 83(5):455-63, 1999 Nov.
- 254 Hindmarch I. Shamsi Z. Stanley N. Fairweather DB. A double-blind, placebo-controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function. *British Journal of Clinical Pharmacology*. 48(2):200-6, 1999 Aug.
- 255 Renwick AG. The metabolism of antihistamines and drug interactions: the role of cytochrome P450 enzymes. *Clinical & Experimental Allergy*. 29 Suppl 3:116-24, 1999 Jul.
- 256 Kay GG. Harris AG. Loratadine: a non-sedating antihistamine. Review of its effects on cognition, psychomotor performance, mood and sedation. *Clinical & Experimental Allergy*. 29 Suppl 3:147-50, 1999 Jul.
- 257 Hey JA. Affrime M. Cobert B. Kreutner W. Cuss FM. Cardiovascular profile of loratadine. *Clinical & Experimental Allergy*. 29 Suppl 3:197-9, 1999 Jul.
- 258 Mason J. Reynolds R. Rao N. The systemic safety of fexofenadine HCl. *Clinical & Experimental Allergy*. 29 Suppl 3:163-70; discussion 171-3, 1999 Jul.
- 259 Mattila MJ. Paakkari I. Variations among non-sedating antihistamines: are there real differences?. *European Journal of Clinical Pharmacology*. 55(2):85-93, 1999 Apr.
- 260 Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *British Journal of Clinical Pharmacology*. 47(3):307-13, 1999 Mar.
- 261 DuBuske LM. Second-generation antihistamines: the risk of ventricular arrhythmias. *Clinical Therapeutics*. 21(2):281-95, 1999 Feb.
- 262 Juniper EF. Rhinitis management: the patient's perspective. *Clinical & Experimental Allergy*. 28 Suppl 6:34-8, 1998 Dec.
- 263 Juniper EF. Rhinitis management: the patient's perspective. *Clinical & Experimental Allergy*. 28 Suppl 6:34-8, 1998 Dec.
- 264 Nicholson AN. Turner C. Central effects of the H1-antihistamine, cetirizine. *Aviation Space & Environmental Medicine*. 69(2):166-71, 1998 Feb.
- 265 Pagliara A. Testa B. Carrupt PA. Jolliet P. Morin C. Morin D. Urien S. Tilletent JP. Rihoux JP. Molecular properties and pharmacokinetic behavior of cetirizine, a zwitterionic H1-receptor antagonist. *Journal of Medicinal Chemistry*. 41(6):853-63, 1998 Mar 12.
- 266 Kay GG. Berman B. Mockoviak SH. Morris CE. Reeves D. Starbuck V. Sukenik E. Harris AG. Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Archives of Internal Medicine*. 157(20):2350-6, 1997 Nov 10.
- 267 Is my antihistamine safe?. *Home Care Provider*. 2(3):117-20, 1997 Jun.
- 268 Valk PJ. Simons RM. Struyvenberg PA. Kruit H. van Berge Henegouwen MT. Effects of a single dose of loratadine on flying ability under conditions of simulated cabin pressure. *American Journal of Rhinology*. 11(1):27-33, 1997 Jan-Feb.

- 269 Nightingale SL. From the Food and Drug Administration. *JAMA*. 277(5):370, 1997 Feb 5.
- 270 Nightingale CH. Treating allergic rhinitis with second-generation antihistamines. *Pharmacotherapy*. 16(5):905-14, 1996 Sep-Oct.
- 271 Simons FE. Learning impairment and allergic rhinitis. *Allergy & Asthma Proceedings*. 17(4):185-9., 1996 Jul-Aug.
- 272 O'Hanlon JF. Ramaekers JG. Antihistamine effects on actual driving performance in a standard test: a summary of Dutch experience, 1989-94. *Allergy*. 50(3):234-42, 1995 Mar.
- 273 Witek TJ Jr. Canestrari DA. Miller RD. Yang JY. Riker DK. Characterization of daytime sleepiness and psychomotor performance following H1 receptor antagonists. *Annals of Allergy, Asthma, & Immunology*. 74(5):419-26, 1995 May.
- 274 Schweitzer PK. Muehlbach MJ. Walsh JK. Sleepiness and performance during three-day administration of cetirizine or diphenhydramine. *Journal of Allergy & Clinical Immunology*. 94(4):716-24, 1994 Oct.
- 275 Tharion WJ. McMenemy DJ. Rauch TM. Antihistamine effects on the central nervous system, cognitive performance and subjective states. *Neuropsychobiology*. 29(2):97-104, 1994.
- 276 Philpot EE. Brooker AE. Biegalski CS. Effects of sedating and nonsedating antihistamines on flying performance. *Military Medicine*. 158(10):654-60, 1993 Oct.
- 277 Rice VJ. Snyder HL. The effects of Benadryl and Hismanal on psychomotor performance and perceived performance. *Aviation Space & Environmental Medicine*. 64(8):726-34, 1993 Aug.
- 278 Passalacqua G. Scordamaglia A. Ruffoni S. Parodi MN. Canonica GW. Sedation from H1 antagonists: evaluation methods and experimental results. *Allergologia et Immunopathologia*. 21(2):79-83, 1993 Mar-Apr.
- 279 Feldman W. Shanon A. Leiken L. Ham-pong A. Peterson R. Central nervous system side-effects of antihistamines in schoolchildren. *Rhinology - Supplement*. 13:13-9, 1992 Sep.
- 280 Gengo FM. Gabos C. Mechtler L. Quantitative effects of cetirizine and diphenhydramine on mental performance measured using an automobile driving simulator. *Annals of Allergy*. 64(6):520-6, 1990 Jun.
- 281 Moskowitz H. Burns M. Effects of terfenadine, diphenhydramine, and placebo on skills performance. *Cutis*. 42(4A):14-8, 1988 Oct 27.
- 282 Gengo FM. Gabos C. Antihistamines, drowsiness, and psychomotor impairment: central nervous system effect of cetirizine. *Annals of Allergy*. 59(6 Pt 2):53-7, 1987 Dec.
- 283 Hindmarch I. Bhatti JZ. Psychomotor effects of astemizole and chlorpheniramine, alone and in combination with alcohol. *International Clinical Psychopharmacology*. 2(2):117-9, 1987 Apr.
- 284 Cohen AF. Hamilton MJ. Peck AW. The effects of acrivastine (BW825C), diphenhydramine and terfenadine in combination with alcohol on human CNS performance. *European Journal of Clinical Pharmacology*. 32(3):279-88, 1987.
- 285 Nicholson AN. Central effects of H1 and H2 antihistamines. *Aviation Space & Environmental Medicine*. 56(4):293-8, 1985 Apr.
- 286 Wilson D. Experience with drugs and driving in Queensland, Australia. *Medicine, Science & the Law*. 25(1):2-10, 1985 Jan.
- 287 Cohen AF. Posner J. Ashby L. Smith R. Peck AW. A comparison of methods for assessing the sedative effects of diphenhydramine on skills related to car driving. *European Journal of Clinical Pharmacology*. 27(4):477-82, 1984.
- 288 Franks HM. Hensley VR. Hensley WJ. Stamer GA. Teo RK. The interaction between ethanol and antihistamines. 1: Dexchlorpheniramine. *Medical Journal of Australia*. 1(8):449-52, 1978 Apr 22.
- 289 Saario I. Linnoila M. Effect of subacute treatment with hypnotics, alone or in combination with alcohol, on psychomotor skills related to driving. *Acta Pharmacologica et Toxicologica*. 38(4):382-92, 1976 Apr.
- 290 Pratt CM. Hertz RP. Ellis BE. Crowell SP. Louv W. Lemuel M. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the counter antihistamines, ibuprofen and clemastine. *American Journal of Cardiology*. 73(2):346-352, 1994 Feb 15.
- 291 Petitti DB. Meta-Analysis decision analysis and cost-effectiveness analysis. Oxford, New York, Oxford University Press, 1994.

Appendix A

Evidence Tables

Evidence Table 1. Efficacy and Toxicity of Cetrizine vs Placebo

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes				
				Groups	Cet	Placebo		
9 Rajaram S., et al. Indian Journal of Pharmacology. 1994	True Randomization Concealed Blinding Intent to Tx Perennial Rhinitis Age: 14-45 years N = 51	NC NC Y Y In the present study, the efficacy and tolerability of a single daily oral dose of cetirizine (10 mg) were assessed in patients with the symptoms of perennial allergic rhinitis and compared with oral astemizole (10 mg) and placebo treatments.	Antigen Source: Natural Exposure* Pollen Season: Not Considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 2 wks and 4 wks Evaluator: Patient Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response + Percent Symptoms Baseline† Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%)	Cet 17 10 qd 4wks 12 70.6% 9.3 4.3 42.7% 11.8% 17.6%	Placebo 16 qd 4wks 4 25.0% 9.6 7.5 0% 6.3%		
38 Falliers CJ., et al. Annals of Allergy. 1991	True Randomization Concealed Blinding Intent to Tx Seasonal Rhinitis Age: >18 years N = 415	NC NC Y Y To compare the efficacy and safety of three once-daily dosing regimens of cetirizine with placebo in patients with documented seasonal allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: No Data for Evaluation: Average of 7 days Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%)	Cet 104 10 bid 7d 51 49% 11.1 4.6 40.3% 25.0% 48.1%	Cet 106 10 qd 7d 37 48% 11.5 5.5 28.6% 22.6% 51.2%	Cet 102 5 qd 7d 37 36% 11.3 5.6 27.3% 8.8% 29.4%	Placebo 103 bid 7d 20 19% 11.3 7.7 5.8% 28.2%
51 Mansmann HC., et al. Annals of Allergy 1992	True Randomization Concealed Blinding Intent to Tx Perennial Rhinitis Age: >18 years N = 216	Y NC Y Y In addition, because cetirizine is effective in single daily doses and causes few side effects, it is an excellent candidate for prolonged use. To investigate this, a double-blind, placebo controlled trial was undertaken to assess the safety and efficacy of cetirizine in alleviating the symptoms of perennial allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: No Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of 4 weeks Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Symptoms Reduction STD Percent Reduction Sedation (%) All ADR (%)	Cet 68 20 qd 4wks 37 54% 9.13 5.3 23.2% 22.5% 71.8%	Cet 72 10 qd 4 wks 35 49% 8.83 5.0 27.5% 15.3% 63.9%	Placebo 70 qd 4wks 19 27% 8.9 6.9 16.4% 50.7%	

Evidence Table 1. Cont.

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes
59 Panayotopoulos SM., et al. Annals of Allergy. 1990	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: Adults N = 16	To correlate the therapeutic efficacy of cetirizine in allergic rhinoconjunctivitis of patients monosensitized to olive pollen with concentrations of this pollen in the atmosphere during one whole season	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: 40-200 particles/m ³ Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 6 weekly scores Evaluator: Patient Placebo Lead-In: No	Groups Cet Placebo N 8 8 Dose (mg) 10 10 Sig: qd 4wks qd 4wks Global Response 6 1 Percent 75.0% 12.5% Symptoms Baseline Ave Symptoms Score 2.3 5.5 STD Percent Reduction 58.0%
80 Wasserman SL., et al. Clinical Therapeutics 1991	True Randomization NC Concealed N Blinding Y Intent to Tx N Seasonal Rhinitis Age: 18-79 years N = 88	This report describes a study of the efficacy and safety of cetirizine and patients with seasonal allergic rhinitis. In particular, we investigated the effect of several different dosing regimens on the drug's efficacy and safety.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: No Data for Evaluation: Average of 2 weeks Evaluator: Patient Placebo Lead-In: No	Groups Cet Cet Cet Placebo N 22 21 22 22 22 Dose (mg) 10 10 5 5 5 Sig: q AM 14d q HS 14d bid 14d bid 14d Symptoms Baseline 11.1 11.3 11.3 11.0 Ave Symptoms Score 3.3 4.0 4.5 5.7 STD Percent Reduction 42.1% 29.8% 21.1% 23% Sedation (%) 14% 14% 29% All ADR (%) 46% 38% 44% 46%
122 Day JH., et al. Annals of allergy, Asthma, & Immunology 1997	True Randomization NC Concealed NC Blinding Y Intent to Tx N Seasonal Rhinitis Age: 14-70 years N = 115	To compare the time to onset for clinically important relief of seasonal allergic rhinitis symptoms for each of the study groups. The secondary objective was to compare the relative efficacy of single doses of the aforementioned drugs in controlling the symptoms of seasonal allergic rhinitis.	Antigen Source: Environment Exposure Unit** Pollen Season: Induced Pollen Count: 5000 grains/m ³ Symptom Score: 5 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of 5 hours Evaluator: Patient Placebo Lead-In: No	Groups Cet Lor Placebo N 23 22 22 Dose (mg) 10 10 10 Sig: once once once Global Response 13 7 4 Percent 57.0% 32.0% 20.0% Sedation (%) 13% 0.0% 14% All ADR (%) 1.7% 0.09% 2.7%

Evidence Table 1. Cont.

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes																																																		
200 Meltzer EO, et al Journal of Allergy & Clinical Immunology 1996	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: >18 years N = 279	The efficacy, duration and onset of action, and safety of cetirizine, 10 mg once daily, was compared with that of loratadine 10 mg once daily and placebo in a field study of patients with seasonal allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: 26-227/m ³ Symptom Score: 6 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of 2 days Evaluator: Patients Placebo Lead-In: No	<table border="1"> <thead> <tr> <th>Groups</th> <th>Cet</th> <th>Lor</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>93</td> <td>93</td> <td>93</td> </tr> <tr> <td>Dose (mg)</td> <td>10</td> <td>10</td> <td>10</td> </tr> <tr> <td>Sig:</td> <td>qd 2d</td> <td>qd 2d</td> <td>qd 2d</td> </tr> <tr> <td>Global Response</td> <td>67</td> <td>52</td> <td>54</td> </tr> <tr> <td>Percent</td> <td>73.6%</td> <td>56.5%</td> <td>59.3%</td> </tr> <tr> <td>Symptoms Baseline</td> <td>21.1</td> <td>20.5</td> <td>18.6</td> </tr> <tr> <td>Ave Symptoms Score</td> <td>11.2</td> <td>13.0</td> <td>12.6</td> </tr> <tr> <td>STD</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Percent Reduction</td> <td>11.1%</td> <td>-3.2%</td> <td></td> </tr> <tr> <td>Sedation (%)</td> <td>12.9%</td> <td>5.4%</td> <td>2.2%</td> </tr> <tr> <td>All ADR (%)</td> <td>30.1%</td> <td>36.7%</td> <td>33.5%</td> </tr> </tbody> </table>	Groups	Cet	Lor	Placebo	N	93	93	93	Dose (mg)	10	10	10	Sig:	qd 2d	qd 2d	qd 2d	Global Response	67	52	54	Percent	73.6%	56.5%	59.3%	Symptoms Baseline	21.1	20.5	18.6	Ave Symptoms Score	11.2	13.0	12.6	STD				Percent Reduction	11.1%	-3.2%		Sedation (%)	12.9%	5.4%	2.2%	All ADR (%)	30.1%	36.7%	33.5%		
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202 Howarth PH., et al. Journal of Allergy & Clinical Immunology. 1999	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-65 years N = 821	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.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: No Data for Evaluation: Average of 14 days Evaluator: Patients Placebo Lead-in : Yes	<table border="1"> <thead> <tr> <th>Groups</th> <th>Fex</th> <th>Fex</th> <th>Cet</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>202</td> <td>211</td> <td>207</td> <td>201</td> </tr> <tr> <td>Dose (mg)</td> <td>180</td> <td>120</td> <td>10</td> <td>10</td> </tr> <tr> <td>Sig:</td> <td>qd 14d</td> <td>qd 14d</td> <td>qd 14d</td> <td>qd 14d</td> </tr> <tr> <td>Sym Baseline</td> <td>7.4</td> <td>7.2</td> <td>7.3</td> <td>7.3</td> </tr> <tr> <td>Ave Sym Score</td> <td>4.1</td> <td>4.2</td> <td>4.0</td> <td>5.4</td> </tr> <tr> <td>STD</td> <td>2.34</td> <td>2.34</td> <td>2.34</td> <td>2.34</td> </tr> <tr> <td>Percent Reduct</td> <td>24.1%</td> <td>22.2%</td> <td>25.9⁺</td> <td></td> </tr> <tr> <td>Sedation (%)</td> <td>3.0%</td> <td>3.0%</td> <td>6.0%</td> <td>3.0%</td> </tr> <tr> <td>All ADR (%)</td> <td>23.0%</td> <td>23.0%</td> <td>25.0%</td> <td>25.0%</td> </tr> </tbody> </table>	Groups	Fex	Fex	Cet	Placebo	N	202	211	207	201	Dose (mg)	180	120	10	10	Sig:	qd 14d	qd 14d	qd 14d	qd 14d	Sym Baseline	7.4	7.2	7.3	7.3	Ave Sym Score	4.1	4.2	4.0	5.4	STD	2.34	2.34	2.34	2.34	Percent Reduct	24.1%	22.2%	25.9 ⁺		Sedation (%)	3.0%	3.0%	6.0%	3.0%	All ADR (%)	23.0%	23.0%	25.0%	25.0%
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Y= Yes, N=No, NC= Not Clear; Fex = Fexofenadine, Lor = Loratadine, Cet= Cetirizine; STD = Standard Deviation, SEM = Standard Error of the Mean

*All enpanelled patients had mild to moderate rhinitis at start of study and their symptoms were observed after being randomized to treatment or placebo groups.

**Mild to moderate rhinitis was induced and sustained in a controlled chamber and the patients' symptoms were documented after being randomized to treatment or placebo groups.

+The investigators and/or subjects measured the global response on a 4-8 point scale. Responders were subjects who had no symptoms or mild symptoms at a time of evaluation.

† The investigators and/or subjects measured the Symptoms on a 4-10 point scale for each of 5 to 8 symptoms on a daily bases. The reduction is the difference between the daily Symptoms Score after treatment and the Placebo.

Evidence Table 2. Efficacy and Toxicity of Loratadine vs Placebo

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes
21 Bedard PM., et al. Clinical Therapeutics 1992	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-60 years N = 195	To evaluate the onset of action and efficacy of 10 mg of loratadine in the treatment of patients with seasonal allergic rhinitis.	Antigen Source: Natural Exposure* Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Day 3 Evaluator: Physician and Patient Placebo Lead-In: No	Groups Lor Placebo N 91 94 Dose (mg) 10 Sig: qd 3d qd 3d Global Response+ 46 27 Percent 50.0% 29.0% Symptoms Baseline † 15.2 14.9 Symptoms Score 7.71 10.1 STD Percent Reduction 30.7% Sedation (%) 2.0% 1.0% All ADR (%) 14.3% 12.8%
27 Bruttman G., et al. Journal of Allergy & Clinical Immunology 1989	True Randomization Y Concealed NC Blinding NC Intent to Tx Y Seasonal Rhinitis Age: 18-45 years N = 70	To compare the efficacy and safety of a single oral daily dose of loratadine 40 mg, in patients with seasonal allergic rhinitis, with twice daily doses of terfenadine 60 mg or placebo.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: 2000-6500 grains/m ³ Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of day 3 and endpoint Evaluator: Physician Placebo Lead-In: No	Groups Lor Placebo N 23 23 Dose (mg) 40 Sig: qd 14d qd 14d Global Response 13 1 Percent 54.3% 2.0% Symptoms Baseline 9.2 10.0 Ave Symptoms Score 5.22 10.4 STD Percent Reduction 49.8% Sedation (%) 0% 0% All ADR (%) 0% 13.0%
28 Bruttman G., et al. Journal of International Medical Research 1987	True Randomization Y Concealed NC Blinding Y Intent to Tx N Perennial Rhinitis Age: >12 years N = 239	To compare the efficacy and side effect profile of loratadine to that of terfenadine, and other non-sedating antihistamine, and placebo. We undertook a six-center study comparing loratadine (10mg qd) with terfenadine (60 mg bid) and placebo in patients with perennial allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Not Considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 4 weekly and endpoint Evaluator: Physician Placebo Lead-In: No	Groups Lor Placebo N 73 74 Dose (mg) 10 Sig: qd 28d qd 28d Global Response 45 23 Percent 61.6% 30.8% Symptoms Baseline 9.9 10.3 Ave Symptoms Score 4.9 7.1 STD Percent Reduction 31.0% Sedation (%) 2.6% 2.6% All ADR (%) 15.6% 15.4%

Evidence Table 2. Cont.

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes
33 Del Carpio J., et al. Journal of allergy & Clinical Immunology 1989	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: >14 years N = 317	To compare the efficacy of a 10 mg qd dose of loratadine with efficacy of terfenadine, a widely used, non-sedating, antihistamine administered at 60 mg BID and placebo in the treatment of patients with seasonal allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 2wks Evaluator: Physician Placebo Lead-in: No	Groups Lor Placebo N 103 101 Dose (mg) 10 Sig: qd 14d qd 14d Global Response 60 27 Percent 58.3% 26.7% Symptoms Baseline 12.7 12.6 Ave Symptoms Score 6.9 8.2 STD Percent Reduction 15.9% Sedation (%) 9.5% 7.6% All ADR (%) 26.7% 20.9%
35 Dockhorn RJ, et al. Annals of Allergy 1987	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 18-45 years N = 330	To Evaluate and compare the efficacy and safety of loratadine 10 mg OD, clemastine 1 mg BID, and placebo when administered orally in the treatment of patients with seasonal allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of days 3,7,14 and endpoint Evaluator: Physician and Patient Placebo Lead-in: No	Groups Lor Placebo N 108 107 Dose (mg) 10 Sig: qd 14d qd 14d Global Response 55 47 Percent 50.5% 43.5% Symptoms Baseline 11.9 11.7 Ave Symptoms Score 6.0 8.9 STD Percent Reduction 32.7% Sedation (%) 6.3% 4.5% All ADR (%) 29.7% 31.8%
39 Frolund L., et al. Allergy 1990	True Randomization Y Concealed NC Blinding NC Intent to Tx Y Perennial Rhinitis Age: 18-65 years N = 155	To compare the efficacy and safety of loratadine 10 mg once daily, clemastine 1 mg twice daily, and placebo, in outpatients with perennial allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Not considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of days 7, 14, and 21 Evaluator: Patient Placebo Lead-in: No	Groups Lor Placebo N 48 38 Dose (mg) 10 Sig: qd 21d qd 21d Symptoms Baseline 6.4 7.1 Ave Symptoms Score 3.4 6.4 STD Percent Reduction 46.9% Sedation (%) 0% 2.0% All ADR (%) 15.1% 49.0%

Evidence Table 2. Cont.

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes		
				Lor	Placebo	
42 Outkowski A., et al Journal of Allergy & Clinical Immunology 1988	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 14-62 years N = 280	To compare the efficacy and safety of loratadine, administered qd with terfenadine, administered bid and placebo in patients suffering from ragweed hay fever.	Antigen Source: Natural Exposure Pollen Season: Not considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Endpoint Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction	Lor 91 40 qd 14d 48 52.7% 13.8 7.7 23.0%	Placebo 88 qd 14d 27 32.5% 14.1 10.0
44 Horak F., et al Arzneimittel-Forschung 1988	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-70 years N = 275	To further evaluate the efficacy and safety of loratadine. In this 14 day study, loratadine 10 mg once daily was compared to terfenadine 60 mg twice daily and placebo as oral therapy for outpatients with seasonal allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of day 3 and endpoint Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%)	Lor 87 10 qd 14d 58 67% 13.4 6.8 51.4% 4.4% 6.7%	Placebo 80 qd 14d 13 16% 13.5 14.0
57 Oei HD Annals of Allergy 1988	True Randomization Y Concealed NC Blinding Y Intent to Tx N Seasonal Rhinitis Age: 25 ± 10 years N = 65	To compare the time of onset of action and the clinical effectiveness of loratadine and astemizole, both given in a dose of 10 mg once a day for 2 weeks.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of day 3 and endpoint Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%)	Lor 22 10 qd 14d 11 51.5% 12.1 5.3 34.6% 0% 18.2%	Placebo 21 qd 14d 6 28.5% 13.6 8.1

Evidence Table 2. Cont.

RefNum/Author/Source Year	Design/Population		Purpose	Significant Factors	Groups/Outcomes			
					Groups	Lor	Placebo	
74 Skassa-Brocick W., et al Journal of Allergy & Clinical Immunology 1988	True Randomization Concealed Blinding Intent to Tx	NC NC Y N	A double-blind, controlled study compared the safety and efficacy of a lower dosage of loratadine (10 mg qd) with mequitazine (5mg bid) and placebo in the treatment of pollen induced seasonal rhinitis	Antigen Source: Natural Exposure Pollen Season: Not Considered Pollen Count: 15-65/m ³ Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of day 3 and endpoint Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%)	22 10 qd 14d 8 36.4% 10.4 4.9 36.4% 4.6% 9.1%	24 0 qd 14d 0 0% 11.6 7.7 4.2% 37.5%	
113 Dolovich J., et al Annals of Allergy 1994	True Randomization Concealed Blinding Intent to Tx	NC N N N	A randomized, placebo-controlled study of the efficacy and safety of loratadine (10mg once daily) in the prophylactic treatment of seasonal allergic rhinitis was therefore conducted.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of day 3 and endpoint Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%)	58 10 qd 42d 38 65% <2 3.2 7.8% 3.4% 30.5%	60 qd 42d 29 49% <2 3.47 1.7% 28.3%	
122 Day JH., et al Annals of Allergy, Asthma, & Immunology 1997	True Randomization Concealed Blinding Intent to Tx	NC NC Y N	To compare the time to onset for clinically important relief of seasonal allergic rhinitis symptoms for each of the study groups. The secondary objective was to compare the relative efficacy of single doses of the aforementioned drugs in controlling the symptoms of seasonal allergic rhinitis.	Antigen Source: Environment Exposure Unit** Pollen Season: Induced Pollen Count: 5000 grains/m ³ Symptom Score: 5 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of 5 hours Evaluator: Patient Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Sedation (%) All ADR (%)	Cet 23 10 once 13 57.0% 13% 1.7%	Lor 22 10 once 7 32.0% 0.0% 0.09%	Placebo 22 once 4 20.0% 14% 2.7%

Evidence Table 2. Cont.

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes			
				Groups	Cet	Lor	Placebo
189 Day JH., et al. Journal of allergy & Clinical Immunology 1998	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: >16 years N = 202	To better characterize the efficacy and onset of action of cetirizine in a more controlled but clinically relevant setting, this agent was compared with loratadine and placebo in patients with symptomatic seasonal allergic rhinitis undergoing controlled pollen challenge in an environmental exposure unit.	Antigen Source: Environmental Exposure Unit Pollen Season: Induced Pollen Count: 3500 grains/m ³ Symptom Score: 5 to 8 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of 2 days Evaluator: Patient Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction All ADR (%)	Cet 67 10 qd 2d 41 60.9% 18.95 12.0 31.0% 30.0%	Lor 67 10 qd 2d 34 50% 19.00 16.1 7.5% 37.5%	Placebo 68 qd 2d 29 43.1% 19.76 17.4 37.0%
200 Meltzer EO, et al Journal of Allergy & Clinical Immunology 1996	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: >18 years N = 279	The efficacy, duration and onset of action, and safety of cetirizine, 10 mg once daily, was compared with that of loratadine 10 mg once daily and placebo in a field study of patients with seasonal allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: 26-227/m ³ Symptom Score: 6 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of 2 days Evaluator: Patients Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Symptoms Baseline Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%)	Cet 93 10 qd 2d 67 73.6% 21.1 11.2 11.1% 12.9% 30.1%	Lor 93 10 qd 2d 52 56.5% 20.5 13.0 -3.2% 5.4% 36.7%	Placebo 93 qd 2d 54 59.3% 18.6 12.6 2.2% 33.5%

Y= Yes, N=No, NC= Not Clear; Fex = Fexofenadine, Lor = Loratadine, Cet= Cetirizine; STD = Standard Deviation, SEM = Standard Error of the Mean

*All enpanelled patients had mild to moderate rhinitis at start of study and their symptoms were observed after being randomized to treatment or placebo groups.
**Mild to moderate rhinitis was induced and sustained in a controlled chamber and the patients' symptoms were documented after being randomized to treatment or placebo groups.

+The investigators and/or subjects measured the global response on a 4-8 point scale. Responders were subjects who had no symptoms or mild symptoms at a time of evaluation.

† The investigators and/or subjects measured the Symptoms on a 4-10 point scale for each of 5 to 8 symptoms on a daily bases. The reduction is the difference between the daily Symptoms Score after treatment and the Placebo.

Evidence Table 3. Efficacy and Toxicity of Fexofenadine vs Placebo

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes
102 Casale TB., et al. Allergy & Asthma Proceedings 1999	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-65 years N = 861	To confirm the efficacy and safety of once-daily dosing of fexofenadine HCl (120 mg and 180 mg QD) compared with placebo in the treatment of autumn SAR.	Antigen Source: Natural Exposure* Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: No Data for Evaluation: Ave of 14 days Evaluator: Patient Placebo Lead-In: Yes	Groups Fex Fex Placebo N 282 287 292 Dose (mg) 180 120 Sig: qd 14d qd 14d qd 14d Symptoms Baseline 7.7 7.7 7.6 Ave Symptoms Score 6.3 6.4 6.9 SEM 0.1 0.1 0.1 Percent Reduction 8.7% 7.2% Sedation (%) Not Reported All ADR (%) 30.4% 30.0% 30.0%
103 Bronsky EA., et al. Allergy & Asthma Proceedings 1998	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-65 years N = 589	To evaluate the clinical efficacy and safety of fexofenadine HCl (40, 60, and 120 mg bid) compared with placebo in the treatment of fall SAR.	Antigen Source: Natural Exposure Pollen Season: Not Considered Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: No Data for Evaluation: Ave of 14 days Evaluator: Patient Placebo Lead-In: Yes	Groups Fex Fex Fex Placebo N 135 138 135 137 Dose (mg) 120 60 40 Sig: bid 14d bid 14d bid 14d bid 14d Symptoms Baseline 8.4 8.6 8.6 8.6 Ave Symptoms Score 6.3 6.8 6.8 7.4 SEM 0.2 0.2 0.2 0.2 Percent Reduction 15.7% 8.1% 8.1% Sedation (%) Not Reported All ADR (%) 13.5% 13.5% 13.5% 13.6%
124 Bernstein D., et al. Annals of Allergy, Asthma, & Immunology 1997	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-65 years N = 575	To evaluate the efficacy and safety of a range of fexofenadine HCl doses (60, 120, and 240 mg bid) compared with placebo for the treatment of seasonal allergic rhinitis due to ragweed pollen exposure.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 14 days Evaluator: Patient Placebo Lead-In: Yes	Groups Fex Fex Fex Placebo N 144 144 141 141 Dose (mg) 240 120 60 Sig: bid 14d bid 14d bid 14d bid 14d Symptoms Baseline 8.8 9.0 8.8 8.9 Ave Symptoms Score 6.2 6.6 6.2 7.4 SEM 0.2 0.2 0.2 0.2 Percent Reduction 16.2% 10.8% 16.2% Sedation (%) Not Reported All ADR (%) 11.7% 6.9% 14.2% 9.2%

Evidence Table 3. Cont.

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes				
				Groups	Fex	Fex	Placebo	
132 Day JH., et al. Annals of Allergy, Asthma, & Immunology 1997	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-65 years N = 99	To characterize the time to onset of clinically important relief of symptoms of allergic rhinitis in subjects taking single doses of either 60 mg or 120 mg of fexofenadine HCl, or placebo, after exposure to ragweed pollen in a controlled environment. Other objectives were to assess the efficacy and safety of single doses of fexofenadine HCl.	Antigen Source: Environmental Exposure Unit** Pollen Season: Induced Pollen Count: 4800 grains/m ³ Symptom Score: 5 pt Scale Include Nasal Congestion: No Data for Evaluation: Ave of 5 hours Evaluator: Patient Placebo Lead-In: Yes	Groups N Dose (mg) Sig: Global Response Percent Sedation (%) All ADR (%)	Fex 33 120 once 52 67% Not Reported 18.2%	Fex 33 60 once 49 58% 18.2%	Placebo 33 once 24 45% 21.2%	
202 Howarth PH., et al. Journal of Allergy & Clinical Immunology 1999	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 12-65 years N = 821	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.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: No Data for Evaluation: Average of 14 days Evaluator: Patients Placebo Lead-in : Yes	Groups N Dose (mg) Sig: Sym Baseline Ave Sym Score STD Percent Reduct Sedation (%) All ADR (%)	Fex 202 180 qd 14d 7.4 4.1 2.34 24.1% 3.0% 23.0%	Fex 211 120 qd 14d 7.2 4.2 2.34 22.2% 3.0% 23.0%	Cet 207 10 qd 14d 7.3 4.0 2.34 25.9% 6.0% 25.0%	Placebo 201 qd 14d 7.3 5.4 2.34 3.0% 25.0%

Y= Yes, N=No, NC= Not Clear; Fex = Fexofenadine, Lor = Loratadine, Cet= Cetirizine; STD = Standard Deviation, SEM = Standard Error of the Mean

*All enpanelled patients had mild to moderate rhinitis at start of study and their symptoms were observed after being randomized to treatment or placebo groups.
 **Mild to moderate rhinitis was induced and sustained in a controlled chamber and the patients' symptoms were documented after being randomized to treatment or placebo groups.

+The investigators and/or subjects measured the global response on a 4-8 point scale. Responders were subjects who had no symptoms or mild symptoms at a time of evaluation.

† The investigators and/or subjects measured the Symptoms on a 4-10 point scale for each of 5 to 8 symptoms on a daily bases. The reduction is the difference between the daily Symptoms Score after treatment and the Placebo.

Evidence Table 4. Efficacy and Toxicity of Chlorpheniramine vs Terfenadine

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes																																								
111 Brandon ML., et al. Annals of Allergy 1980	True Randomization NC Concealed NC Blinding Y Intent to Tx N Seasonal Rhinitis Age: Adults N = 120	To compare the efficacy and safety of chlorpheniramine vs terfenadine and placebo.	Antigen Source: Natural Exposure* Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 3-4 days Evaluator: Physician Placebo Lead-In: No	<table border="1"> <thead> <tr> <th>Groups</th> <th>Ter</th> <th>Chlor</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>40</td> <td>40</td> <td>40</td> </tr> <tr> <td>Dose (mg)</td> <td>30</td> <td>4</td> <td>qid</td> </tr> <tr> <td>Sig:</td> <td>qid</td> <td>qid</td> <td>qid</td> </tr> <tr> <td>Global Response + Percent</td> <td>21</td> <td>27</td> <td>16</td> </tr> <tr> <td></td> <td>52.5%</td> <td>67.5%</td> <td>40.0%</td> </tr> <tr> <td>Sedation (%)</td> <td>10%</td> <td>23%</td> <td>10%</td> </tr> <tr> <td>All ADR (%)</td> <td>33%</td> <td>40%</td> <td>35%</td> </tr> </tbody> </table>	Groups	Ter	Chlor	Placebo	N	40	40	40	Dose (mg)	30	4	qid	Sig:	qid	qid	qid	Global Response + Percent	21	27	16		52.5%	67.5%	40.0%	Sedation (%)	10%	23%	10%	All ADR (%)	33%	40%	35%								
Groups	Ter	Chlor	Placebo																																									
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111 Brandon ML., et al. Annals of Allergy 1980	True Randomization NC Concealed NC Blinding Y Intent to Tx N Seasonal Rhinitis Age: Adults N = 122	To compare the efficacy and safety of chlorpheniramine vs terfenadine and placebo.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 2 days Evaluator: Physician Placebo Lead-In: No	<table border="1"> <thead> <tr> <th>Groups</th> <th>Ter</th> <th>Chlor</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>42</td> <td>41</td> <td>39</td> </tr> <tr> <td>Dose (mg)</td> <td>100</td> <td>4</td> <td>qid</td> </tr> <tr> <td>Sig:</td> <td>qid</td> <td>qid</td> <td>qid</td> </tr> <tr> <td>Global Response</td> <td>21</td> <td>25</td> <td>21</td> </tr> <tr> <td>Percent</td> <td>50.0%</td> <td>61.0%</td> <td>54.0%</td> </tr> <tr> <td>Sedation (%)</td> <td>14%</td> <td>15%</td> <td>8%</td> </tr> <tr> <td>All ADR (%)</td> <td>24%</td> <td>34%</td> <td>13%</td> </tr> </tbody> </table>	Groups	Ter	Chlor	Placebo	N	42	41	39	Dose (mg)	100	4	qid	Sig:	qid	qid	qid	Global Response	21	25	21	Percent	50.0%	61.0%	54.0%	Sedation (%)	14%	15%	8%	All ADR (%)	24%	34%	13%								
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All ADR (%)	24%	34%	13%																																									
111 Brandon ML., et al. Annals of Allergy 1980	True Randomization NC Concealed NC Blinding Y Intent to Tx N Seasonal Rhinitis Age: Adults N = 137	To compare the efficacy and safety of chlorpheniramine vs terfenadine and placebo.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 5 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 2 days Evaluator: Physician Placebo Lead-In: No	<table border="1"> <thead> <tr> <th>Groups</th> <th>Ter</th> <th>Ter</th> <th>Chlor</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>36</td> <td>31</td> <td>34</td> <td>36</td> </tr> <tr> <td>Dose (mg)</td> <td>200</td> <td>20</td> <td>4</td> <td></td> </tr> <tr> <td>Sig:</td> <td>tid</td> <td>tid</td> <td>tid</td> <td>tid</td> </tr> <tr> <td>Global Response</td> <td>24</td> <td>24</td> <td>24</td> <td>18</td> </tr> <tr> <td>Percent</td> <td>66.7%</td> <td>77.4%</td> <td>70.6%</td> <td>50.0%</td> </tr> <tr> <td>Sedation (%)</td> <td>7%</td> <td>12%</td> <td>17%</td> <td>5%</td> </tr> <tr> <td>All ADR (%)</td> <td>22%</td> <td>14%</td> <td>29%</td> <td>12%</td> </tr> </tbody> </table>	Groups	Ter	Ter	Chlor	Placebo	N	36	31	34	36	Dose (mg)	200	20	4		Sig:	tid	tid	tid	tid	Global Response	24	24	24	18	Percent	66.7%	77.4%	70.6%	50.0%	Sedation (%)	7%	12%	17%	5%	All ADR (%)	22%	14%	29%	12%
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Evidence Table 4. Cont.

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes
139 Melillo G., et al. Arzneimittel-Forschung 1982	True Randomization NC Concealed NC Blinding Y Intent to Tx N Seasonal Rhinitis Age: 13-55 years N = 119	To establish the efficacy of terfenadine in combating the symptoms of allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Not Considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 7 days Evaluator: Patient Placebo Lead-In: Yes	Groups Ter Chlor Placebo N 41 40 38 Dose (mg) 60 4 Sig: bid 7d tid 7d Global Response 29 31 18 Percent 70.0% 77.0% 47.4% Sedation (%) 14.6% 55% 10.0% All ADR (%) Not Reported
235 Brostoff J., et al. Postgraduate Medical Journal. 1982	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Perennial Rhinitis Age: >12 years N = 60	To compare the effects of terfenadine, chlorpheniramine maleate and placebo in patients with perennial or non-seasonal allergic rhinitis.	Antigen Source: Natural Exposure Pollen Season: Not Considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 14 days Evaluator: Patient Placebo Lead-In: No	Groups Ter Chlor Placebo N 20 20 20 Dose (mg) 60 8 Sig: bid 14d bid 14d bid 14d Symptoms Baseline† 7.6 8.0 7.8 Ave Symptoms Score 5.1 4.6 5.8 STD Percent Reduction 12.1% 20.7% Sedation (%) 10% 25% 5% All ADR (%) 38% 53% 20%
236 Backhouse CL, et al. Practitioner 1982	True Randomization NC Concealed NC Blinding Y Intent to Tx Y Seasonal and Perennial Rhinitis Age: >12 years N = 136	To test these observations in general practice in the UK and to compare clinical efficacy and side effects of terfenadine with those of placebo and of the antihistamine which is most commonly used in the UK, chlorpheniramine maleate.	Antigen Source: Natural Exposure Pollen Season: Not Considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 14 days Evaluator: Patient Placebo Lead-In: No	Groups Ter Chlor Placebo N 44 44 45 Dose (mg) 60 8 Sig: bid 7d bid 7d bid 7d Global Response 32 31 12 Percent 72.7% 69.7% 26.6% Sedation (%) 2.2% 25% 4.4%

Y= Yes, N=No, NC= Not Clear; Ter = Terfenadine, Chlor = Chlorpheniramine; STD = Standard Deviation, SEM = Standard Error of the Mean

* All enpanelled patients had mild to moderate rhinitis at start of study and their symptoms were observed after being randomized to treatment or placebo groups.

† The investigators and/or subjects measured the global response on a 4-8 point scale. Responders were subjects who had no symptoms or mild symptoms at a time of evaluation.

‡ The investigators and/or subjects measured the Symptoms on a 4-10 point scale for each of 5 to 8 symptoms on a daily bases. The reduction is the difference between the daily Symptoms Score after treatment and the Placebo.

Evidence Table 5. Efficacy and Toxicity of Cetirizine vs Placebo in Children

Ref Num/Author/Source Year	Design/Population	Purpose	Significant Factors	Groups/Outcomes
1 Baelde Y., et al. Drug Investigations. 1992	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Perennial Rhinitis Age: 2-14 years N = 138	To determine an effective and well tolerated dose of cetirizine for the treatment of chronic allergic rhinitis in children aged from 2 to 14 years	Antigen Source: Natural Exposure* Pollen Season: Not Considered Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of days 3 and 14 Evaluator: Parents Placebo Lead-In: No	Groups N Dose (mg) Sig: Symptoms Baseline † Ave Symptoms Score STD Percent Reduction Sedation (%) All ADR (%) Cet 46 5 bid 14d 13.6 3.29 1 33.8% 0% 8.7% Cet 46 2.5 bid 14d 13.6 4.26 1 14.3% 6.5% 17.4% Placebo 46 bid 14d 13.2 4.97 1 4.3% 17.4%
87 Jobst S., et al. Allergy. 1994	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Perennial Rhinitis Age: 6-12 years N = 330	To assess the efficacy of three dose levels (2.5, 5, and 10 mg) of cetirizine given once daily in children with perennial allergic rhinitis, in order to investigate the dose response relationship of cetirizine administered once a day and to compare the safety of cetirizine with that of placebo in children aged 6-12 years.	Antigen Source: Natural Exposure Pollen Season: No Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Average of scores at days 7 & 14 Evaluator: Physician Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response+ Percent Symptoms Baseline Ave Symptoms Score SE Percent Reduction Sedation (%) All ADR (%) Cet 76 10 qd 14d 50 66.2% 2.6 1.45 1 23.7% Not Reported 22.4% Cet 85 5 qd 14d 56 66.3% 2.75 1.6 15.8% 14.1% Cet 84 2.5 qd 14d 44 51.8% 2.6 1.5 21.1% 25.0% Placebo 83 qd 14d 31 37.6% 2.65 1.9 18.1%
230 Masi M., et al. Pediatric Allergy and Immunology. 1993	True Randomization Y Concealed NC Blinding Y Intent to Tx Y Seasonal Rhinitis Age: 6-12 years N = 124	To obtain further evidence to confirm the efficacy and tolerability of a 10 mg daily dose of cetirizine given as 5 mg twice daily in seasonal allergic rhinoconjunctivitis in children.	Antigen Source: Natural Exposure Pollen Season: Yes Pollen Count: Not Collected Symptom Score: 4 pt Scale Include Nasal Congestion: Yes Data for Evaluation: Ave of 14 days Evaluator: Patient Placebo Lead-In: No	Groups N Dose (mg) Sig: Global Response Percent Sedation (%) All ADR (%) Cet 63 5 bid 14d 49 79% 9.5% 31.8% Placebo 61 bid 14d 30 50% 3.3% 31%

Appendix B

Meta-Analysis

Figure 1. Global Efficacy of Cetirizine for Treatment of Rhinitis

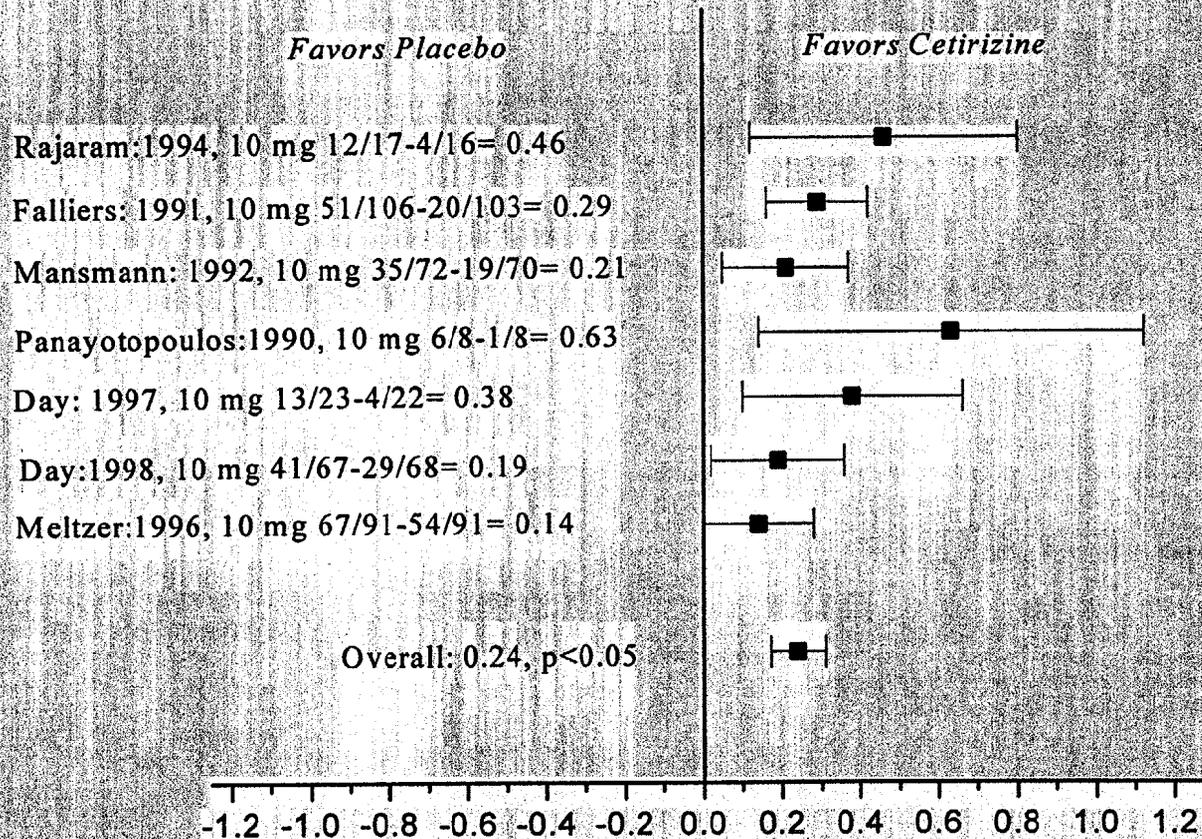


Figure 2. Global Efficacy of Loratadine for Treatment of Rhinitis

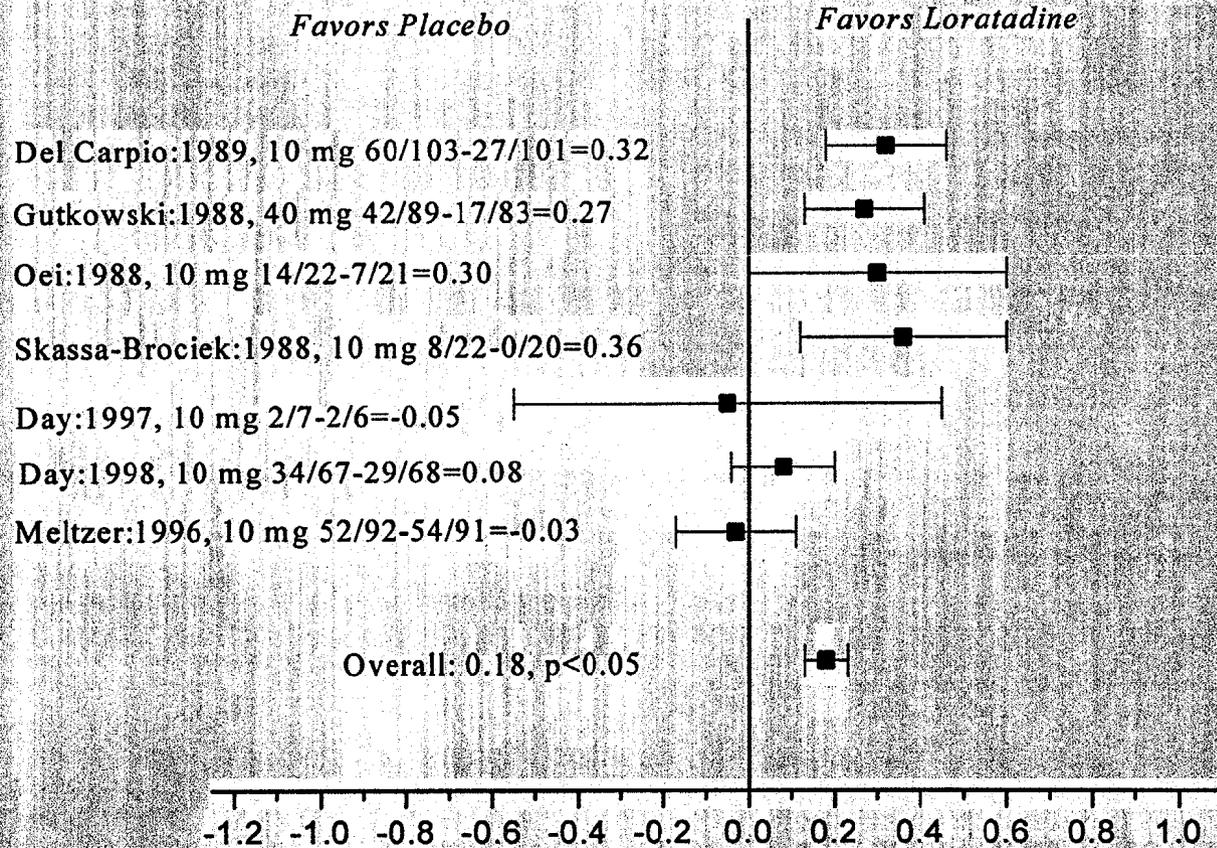
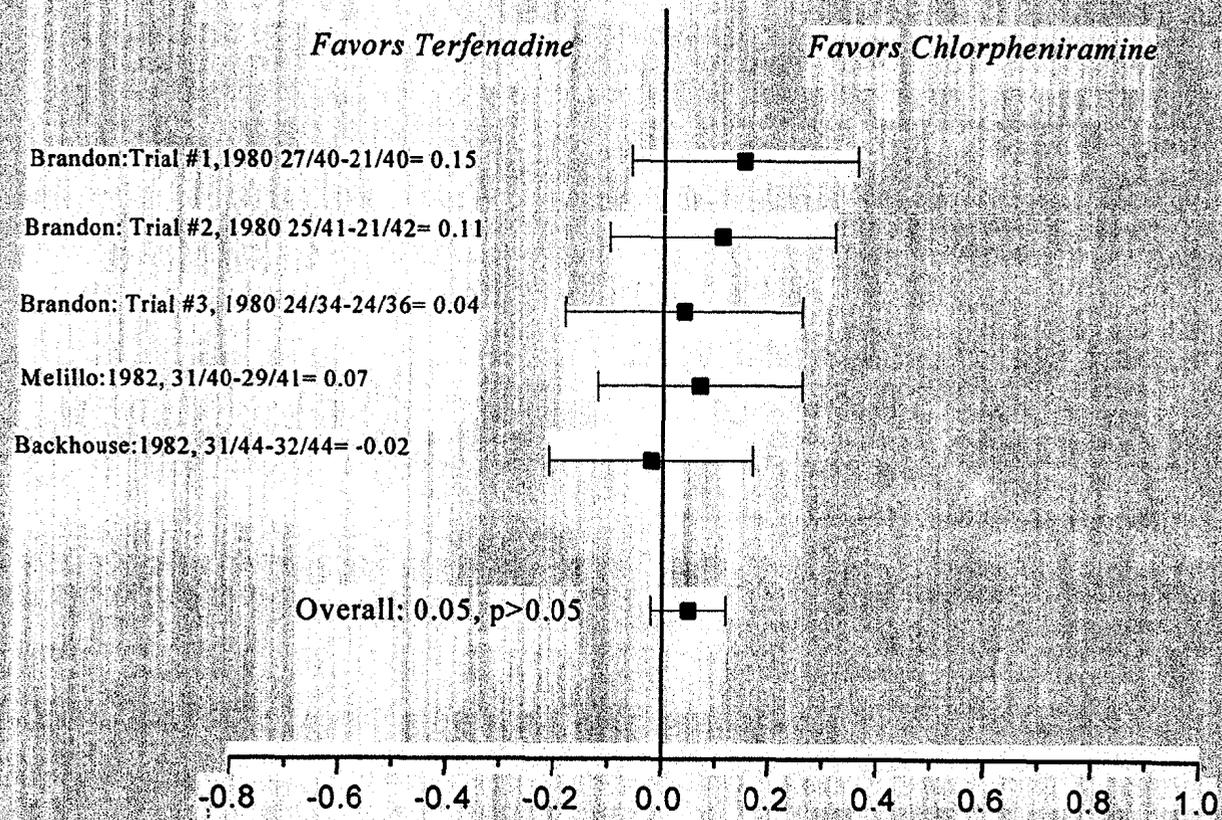
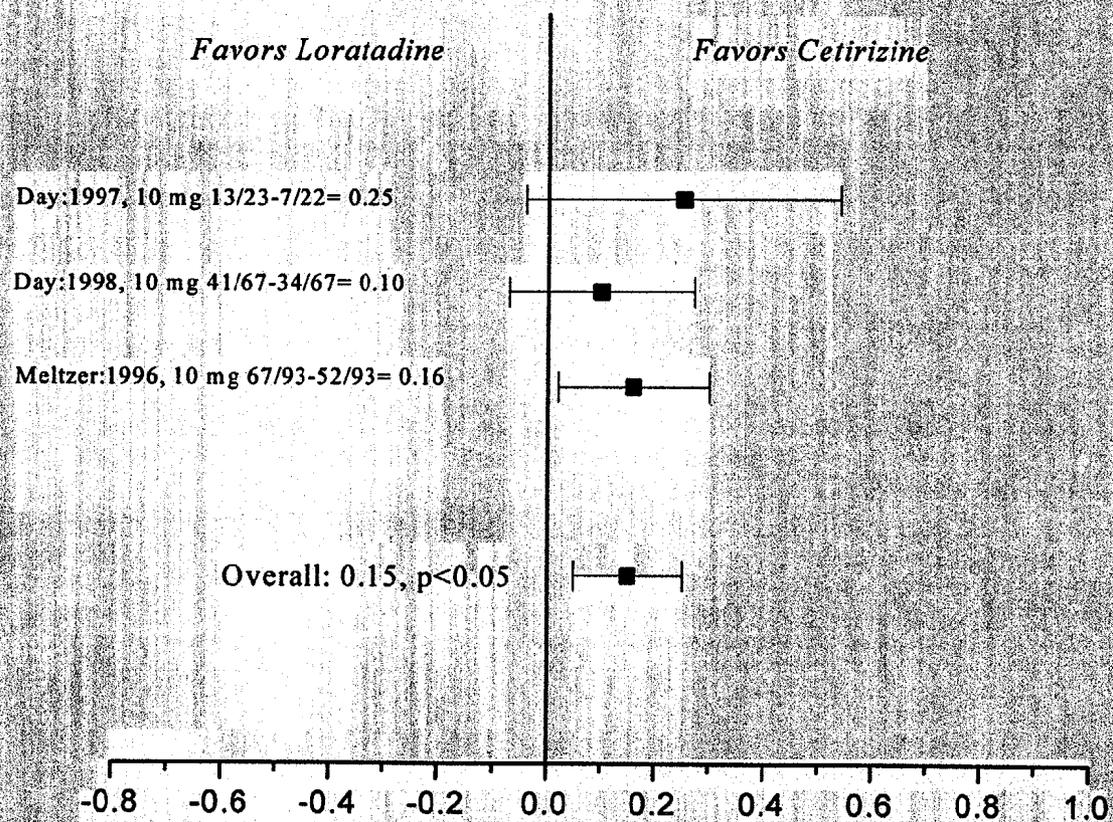


Figure 3. Global Efficacy of Chlorpheniramine vs Terfenadine for the Treatment of Rhinitis



**Figure 4. Global Efficacy of Cetirizine vs Loratadine
for the Treatment of Rhinitis**



**Figure 5. Global Efficacy of Cetirizine vs Placebo
in Children for the Treatment of Rhinitis**

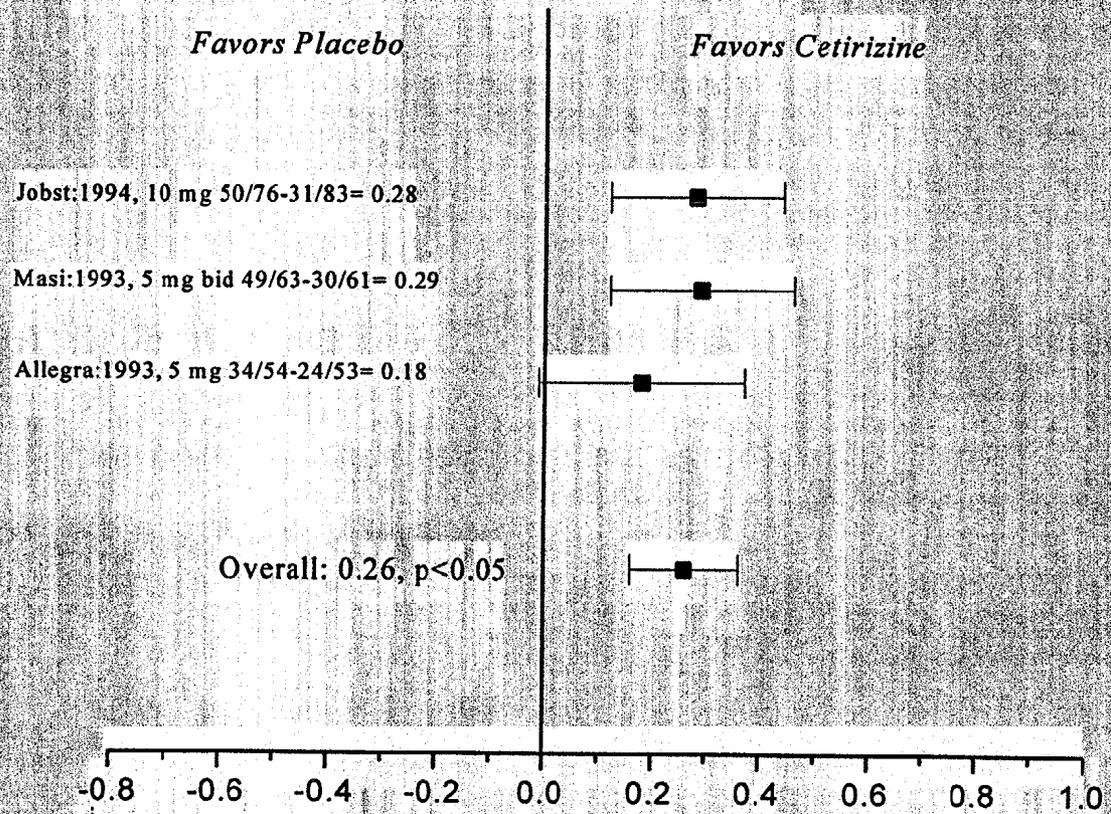
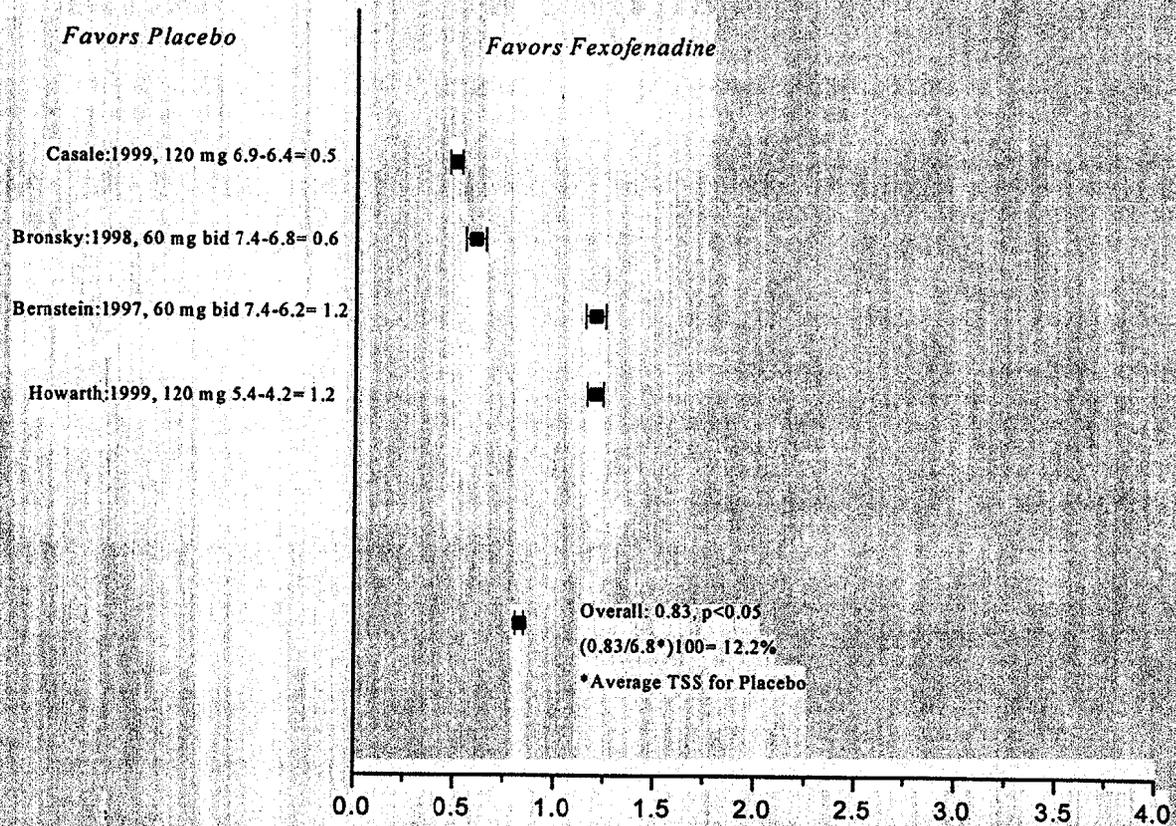


Figure 6. Total Symptom Score Reduction of Fexofenadine for Treatment of Rhinitis



**Figure 7. Total Symptom Score Reduction of Cetirizine
for Treatment of Rhinitis**

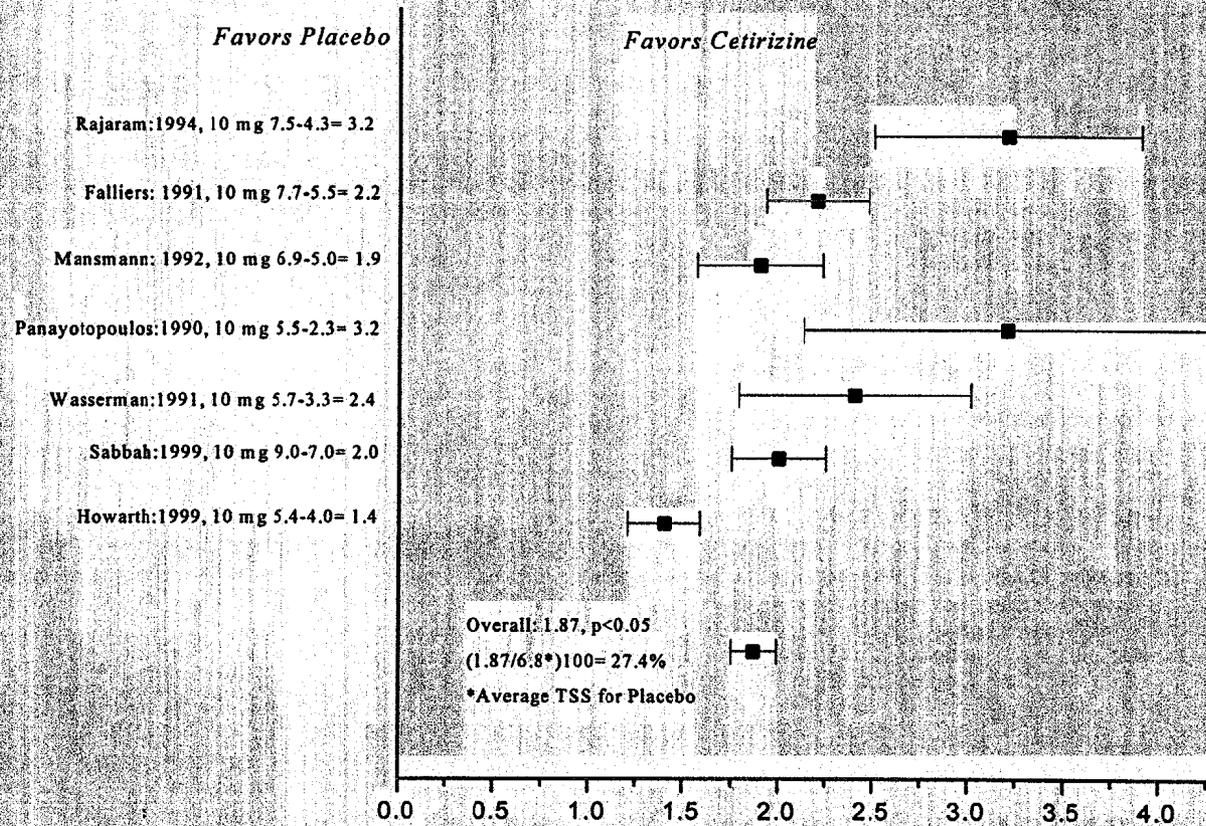


Figure 8. Total Symptom Score Reduction of Loratadine for Treatment of Rhinitis

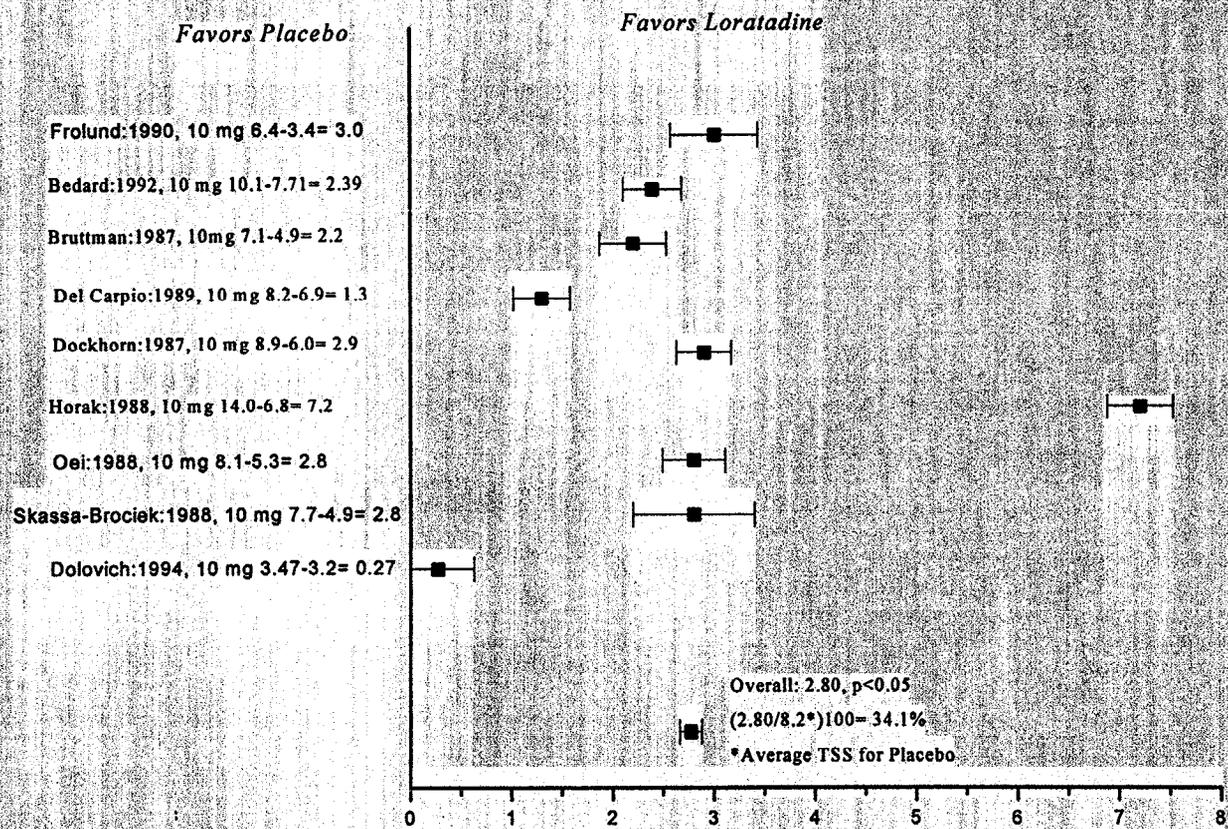


Figure 9. Incidence of Sedation of Cetirizine for Treatment of Rhinitis

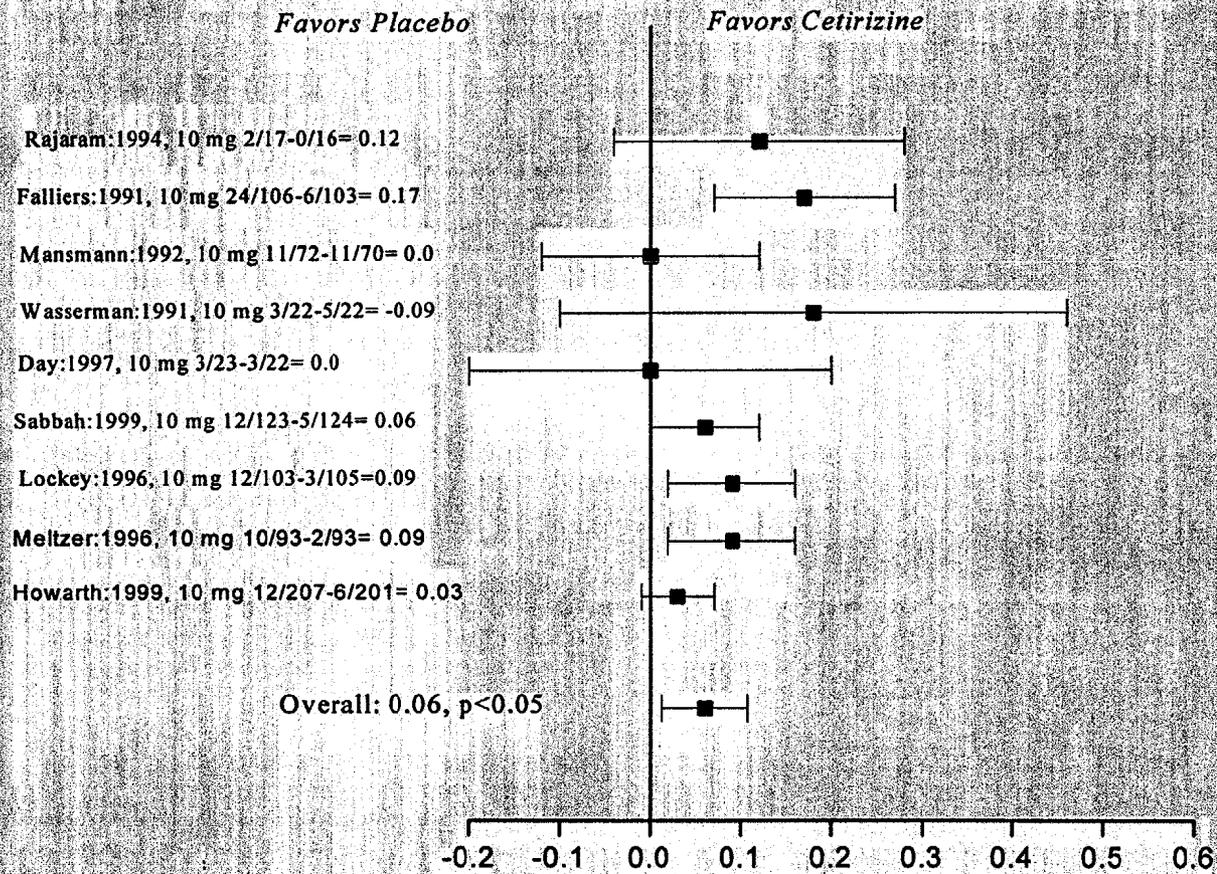
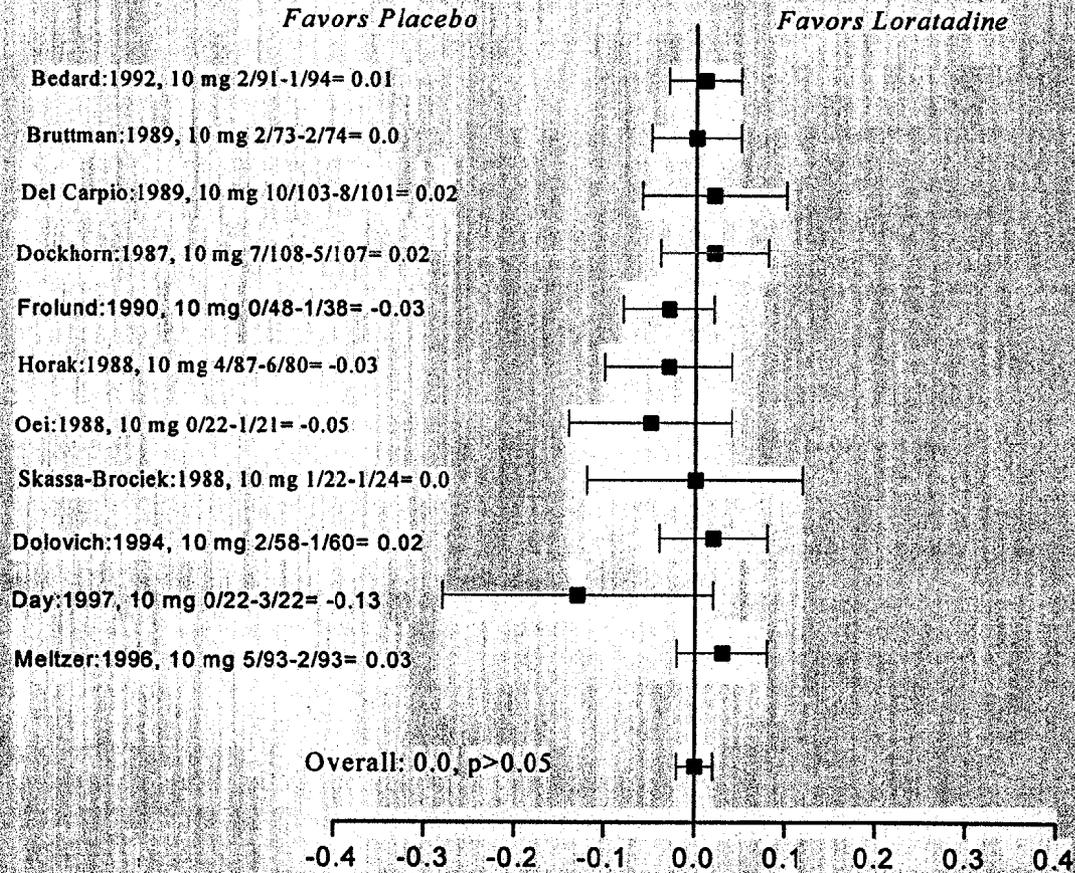
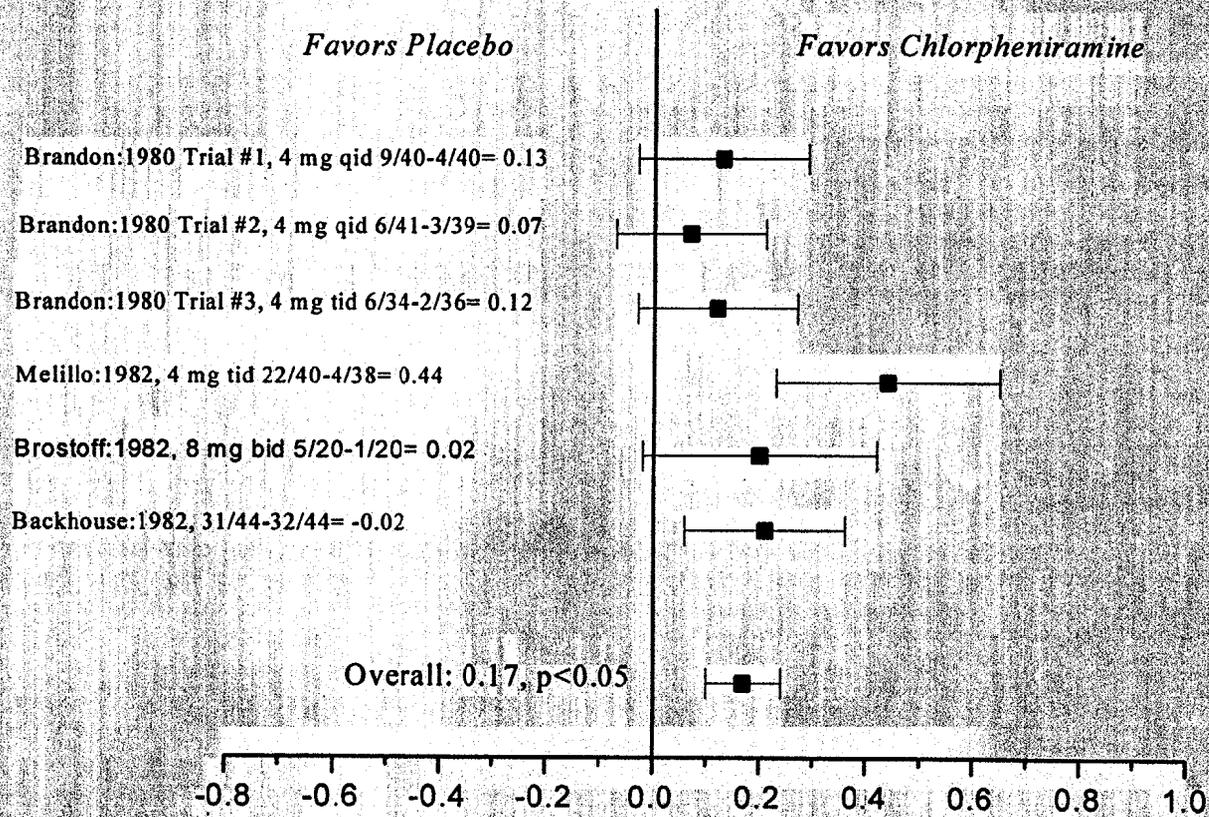


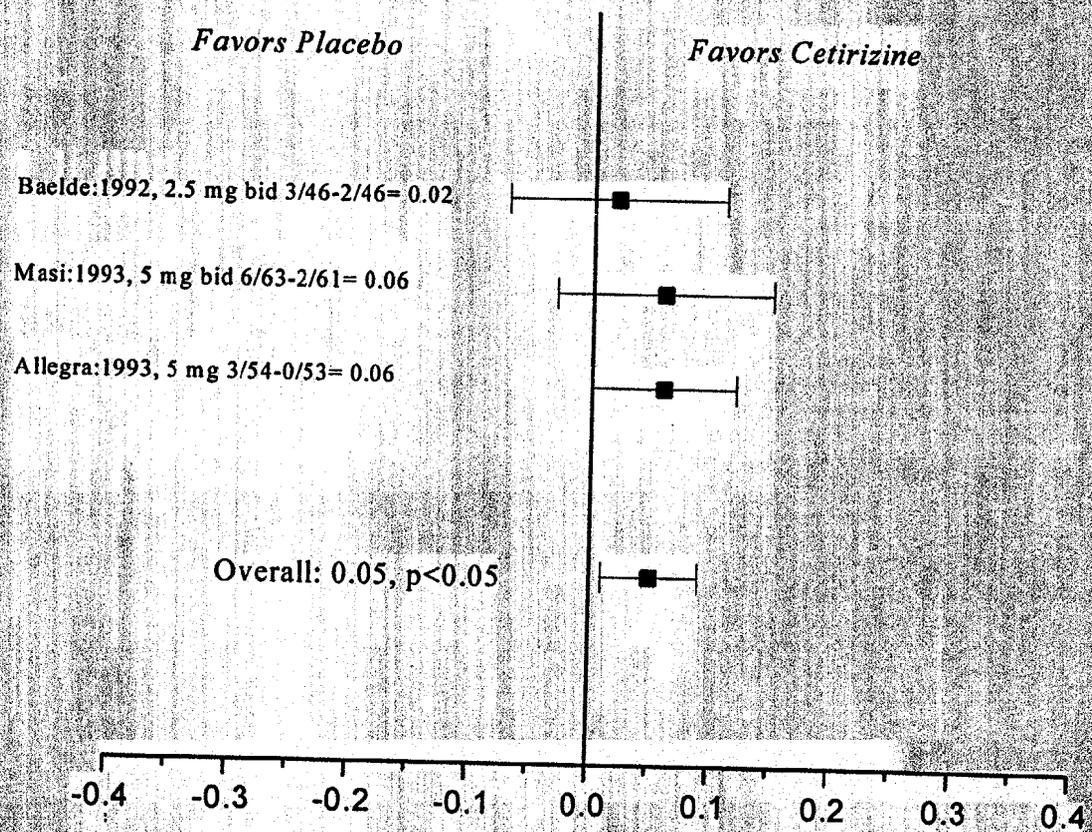
Figure 10. Incidence of Sedation of Loratadine for Treatment of Rhinitis



**Figure 11. Incidence of Sedation of Chlorpheniramine
for the Treatment of Rhinitis**



**Figure 12. Incidence of Sedation of Cetirizine
in Children for the Treatment of Rhinitis**



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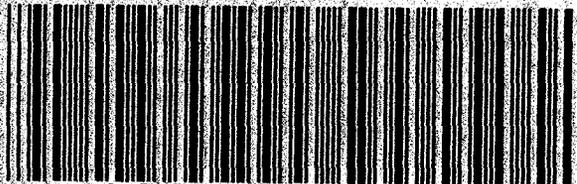
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