Drug Class Review
on
Newer Antihistamines

Final Report Update 1 Evidence Tables
April 2006

Original Report Date: November 2004
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior versions of this report can be accessed at the DERP website.

TABLE OF CONTENTS

Evidence Tables

Funding:
The funding source, the Center for Evidence-based Policy, is supported by 17 organizations, including 15 state Medicaid programs. These organizations selected the topic and had input into the Key Questions for this review. The content and conclusions of the review are entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Placebo-controlled trials			
Okubo 2004, 2005 Japan	Randomized, DB, placebo-controlled, parallel-group, single center	SAR Aged 20-55y with a positive Japanese cedar-pollen-specific IgE test (> class 2 severity), cedar pollinosis symptoms for ≥ 2 y, and reside within the urban area of Tokyo (to ensure equivalent exposure to pollen), and have a TSS (sneezing, nasal discharge, nasal blockage, and itching eyes) >4 with ≥ 2 individual symptoms rated higher than moderate on the second day of study treatment.	Subjects were excluded if they had experienced symptoms before the beginning of the Japanese cedar pollinosis season, had complications of nasal disease (perennial allergic nasal disease, vasomotor rhinitis, acute or chronic non-allergenic rhinitis, acute/chronic sinusitis, or infective rhinosinusitis, infective rhinitis), were traveling abroad during the study period or were deemed ineligible for participation by the investigator (due to cognitive impairment, for example).

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions
Placebo-controlled trials			
Okubo 2004, 2005 Japan	Mean age: 33.5y 58.2% female Ethnicity: NR	F: Fexofenadine 60 mg bid P: placebo bid 14-day treatment period	Any concurrent use of drugs that could influence the evaluation of efficacy was prohibited.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Placebo-controlled trials		
Okubo 2004, 2005 Japan	Japanese versions of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; questions scaled from 0 to 6) and Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS 0"no impairment" to 100% "higher loss of impairment") questionnaire completed during run-in, day 1 of treatment, and at end of 2 week treatment period. WPAI-AS instrument: measures generic and allergy-specific performance impairment in work and classroom productivity and regular activity; range 0-100 Patients also recorded in daily diary symptoms and compliance; rated individual symptoms from 0 to 4 "very severe" Daily TSS: total score of sneezing, runny nose, nasal congestion, itchy eyes, watery eyes; obtained from diary	3/ NR/ 206

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Placebo-controlled trials	
Okubo 2004, 2005 Japan	Results given as F vs P Change RQLQ overall score: -0.45 vs -0.12, p=0.0052 (4 of 7 domains p<0.05 for F vs P) WPAI-AS: overall work impairment decreased 5.5% vs 3.4%, p=0.016 Change in TSS from baseline to day 14: -0.5 vs +0.8, p<0.0001

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Active-controlled trials			
Berger 2003 USA	RCT, DB, placebo-controlled, parallel-group, multi-center	SAR Pts who had a minimum 2-year history of SAR and a documented (+) allergy skin test result during the previous year.	Pts were excluded from participation for any of the following reasons: use of concomitant medications that could affect the evaluation of efficacy; any medical or surgical condition that could affect the metabolism of the study medications; having clinically significant nasal disease other than seasonal allergic rhinitis or significant nasal structural abnormalities; having respiratory infection or other infection requiring antibiotic therapy within 2 w of beginning the baseline screening period; having significant pulmonary disease and/or active asthma requiring daily medication; and history of or current alcohol or drug abuse. Women of childbearing potential who were not abstinent or practicing an accepted method of contraception and women who were pregnant or nursing were excluded from participation.
Bernstein 2004 USA	RCT, ACT, DB, Parallel Multicenter	SAR Eligible pts were ≥ 12y with a history of allergic rhinitis for ≥ 2 y and a positive skin test to ≥1 allergen relevant to the spring pollen season and geographic region. Pts had a total ocular SS (TOSS) of ≥ 120 (out of 300) (ocular itching, tearing, redness) and a nasal congestion score of ≥ 50/100 on at least 4 of 7 days preceding visit 2.	NR
Bhatia 2005 USA	RCT, ACT, DB, Parallel Multicenter	SAR Pts 18y-45y with a clinical history of sensitivity to tree or grass pollens with a positive skin test result during the spring season for the past 2years. Participants had to be symptomatic owing to their allergies to be enrolled.	Pts who had used systemic corticosteroids in previous 30d, oral antihistamines or decongestants in past 7d, topical antihistamines or decongestants in past 24h, who were using long-term anti-asthma medication or who had received immunotherapy in previous 2 y. Women were excluded if they were pregnant or nursing; had to have a negative urine pregnancy test

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions
Active-controlled trials			
Berger 2003 USA	Age: 35, range 12-79 66% female 80% white	D: desloratadine 5 mg A1: azelastine nasal A2: azelastine nasal + loratadine P: placebo	All concomitant medications were discontinued for protocol-specified times, based on the elimination half-life of each drug, before beginning the double-blind treatment period.
Bernstein 2004 USA	NR for whole population 80% of pts between 18-64y 38-42% male/ group 80-89%Caucasian/group	L: loratadine 10 mg po + placebo spray F: Fluticasone propionate 0.20 mg spray + placebo tablet P: placebo (spray+ capsule) 28-day treatment period	No
Bhatia 2005 USA	Mean age: 26.0y 45.9% male White: 67.2%	14 day treatment D: Desloratadine 5 mg po + placebo spray B: Budesonide 64 microgram spray + placebo	Acetaminophen, birth control pills, Depo-Provera, or as-needed bronchodilators only

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Active-controlled trials		
Berger 2003 USA	Pts scored severity of symptoms (runny nose, sneezing, itchy nose, and nasal congestion) in daily diary cards using a rating scale 0 (no symptoms) to 3 (severe).	0/0/61
Bernstein 2004 USA	Pt VAS for TOSS (ocular itching, tearing, and redness; indiv. symptoms scored 0 = none to 100 = most severe) with range: 0-300points Pt VAS nasal congestion, 0-100 Diary card collected at clinic visit day 15 and 29 Pt evaluated improvement, 7 pt scale	53 /NR / 471
Bhatia 2005 USA	Rhinoconjunctivitis Quality of Life Questionnaire (RQoLQ): 7 domains scored and averaged Symptom diary: sneezing, runny nose, stuffy nose, itchy eyes/nose: 0 "no symptoms" to 3 "severe" for 4 individual symptoms; total daily score: 0-24	0/0/61

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Active-controlled trials	
Berger 2003 USA	% improvement from baseline in TNSS: (p-values between active treatments not reported) F: 17.5% (p=0.039 vs P) A1: 21.9% (p<0.001 vs P) A2: 21.5% (p<0.001 vs P) P: 11.1%
Bernstein 2004 USA	Results given as L vs F vs P Mean change scores from baseline to day 28: TOSS total score : -72.5 vs -88.7 vs -59.5 (p<0.05 for F vs L) (indiv. scores for itching, tearing, redness, all showed larger decrease for F vs L (p<0.05) Nasal congestion: -25.0 vs -35.5 vs -21.7 (p<0.05 for F vs L) Individual ocular scores: F showed greater mean change vs both L (p=0.045) and P (p<0.001) Pt evaluated response: % reporting improvement: 64% vs 82% vs 65% (p<0.05 for F vs L; NSD L vs P)
Bhatia 2005 USA	Results given as D vs B Total nasal peak inspiratory flow improvement, (summing all values) B>D days 1-4 and 7-12, p<0.05 Morning: B had a significant increase from baseline days 8,10,12; D days 1-12 (p<0.05); B>D 8 of 12 days (p<0.05) Evening: B>D days 5 , 8-12 (p<0.05) Average change in total RQoLQ: -1.5 vs -2.0 (on scale 0-6, 6=worse), NSD between groups Individual symptoms: NSD between groups

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Corren 2005 USA	RCT, ACT, DB, Parallel Multicenter	SAR Male and female pts ≥ 12y with at least a 2 y history of SAR and a documented positive allergy skin test, either intradermal or epicutaneous, during the previous year. PTS had to have TSS ≥ 8 (of max. 24)and a nasal congestion score of ≥ 2 (max. 3) over previous 12h prior to study entry.	Use of concomitant medication that could affect the assessment of efficacy of study treatment; any medical or surgical condition that could affect the metabolism of study medications; clinically significant nasal disease (other than SAR) or significant nasal structural abnormalities; respiratory infection or other infection requiring antibiotic therapy within 2 weeks of the single-blind placebo lead-in; past or current alcohol or drug abuse; and significant pulmonary disease, including persistent asthma requiring use of controller medication. Women of childbearing potential not using an accepted method of contraception and women who were pregnant or nursing were excluded.
Dockhorn 1987 USA	RCT, DB, placebo-controlled, multi-center	SAR Each pts hypersensitivity to spring pollen was confirmed by allergy history and a (+) response to skin testing (prick method) with extracts from prevalent spring pollens indigenous to the living area. The antigen-induced wheal diameter was to be at least 3 mm greater than that induced by the diluent control, measured 15-30 min following exposure.	Pts were excluded from the study according to the following criteria: women of childbearing potential; documented history of asthma within the previous 2 y; immunotherapy with pollen extracts started within the previous 12 m; any significant current disease which, in the judgment of investigator, would have interfered with the study; a clinically significant abnormal screening laboratory test result; multiple drug allergies or history of idiosyncratic reactions to antihistamines; use of any investigational drug within the previous month.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions
Corren 2005 USA	Mean age: 35.6y Range: 12-74y 38.1% Male White: 69.7% Black: 19.2% Asian: 2.9% Other: 8.1%	C: Cetirizine 10 mg po QAM + placebo spray bid A: Azelastine nasal spray, 2 sprays /nostril bid + placebo tablet qam 14-day treatment period	No
Dockhorn 1987 USA	Age: 32, range 12-65 79% male 93% white	L: loratadine 10 mg C: clemastine 2 mg P: placebo	Concomitant use of any antihistamine, investigational drug, or any drug which could have an effect on the signs and symptoms of SAR, or which could interact with study drugs was prohibited.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Corren 2005 USA	TSS total and individual symptom scores: nasal itching, nasal congestions, runny nose, sneezing (total: 0-24; indiv: 0-3), measured on days 0, 2, and 14 RQoLQ (rhino conjunctivitis Quality of Life Questionnaire) change from baseline to Day 14 (range of score not given)	8/ 1/ 306 for efficacy, 307 for safety
Dockhorn 1987 USA	Diaries were issued in which pts were to record daily severity of allergy symptoms and any other relevant comments. These were returned on days 3, 7, and 14 of treatment for investigator evaluation of drug efficacy and safety. Evaluation of efficacy was based on investigator and pt assessment of nasal (nasal discharge, nasal stuffiness, nasal itching, sneezing) and non nasal (itching or burning eyes, tearing eyes, redness of eye, itching of ears or palate) symptoms, overall condition of rhinitis, and therapeutic response to treatment. The severity of each symptom was scored on a scale of 0 (no symptoms) to 3 (severe). The overall condition of rhinitis used the same 0-3 scale. The therapeutic response was evaluated on treatment days 3, 7, 14 using a scale 1 (excellent response) to 5 (no response).	46/NR/286

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Corren 2005 USA	Data given as C vs A % change in TSS score between baseline and Day 14 (% improvement) For TNSS total: 23.0% vs 29.3%, p=0.015 for A vs C. Itchy nose: 21.7% vs 29.5%, p=0.056 for A vs C Nasal congestion: 18.1% vs 21.1%, NSD Runny nose: 19.6% vs 29.8%, p=0.003 for A vs C Sneezing: 28.2% vs 33.8%, p=0.065 for A vs C Overall mean change of RQoLQ scores from baseline: 1.11 vs 1.41, p = 0.049 for A vs C Individual QOL domains: improved from baseline in both C and A, NSD between groups on any of the individual domains
Dockhorn 1987 USA	NS between active treatments L vs C vs P: -49% vs -46% vs 23%

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Hampel 2004 USA	RCT, active and placebo control groups, DB, parallel group Multicenter	SAR Pts aged 12-70 y with ≥ 2 yr history of ragweed SAR characterized by the following symptoms: nasal congestion, rhinorrhea, sneezing, and nasal itching, a positive skin prick test to ragweed allergen within 1y before enrollment, a minimum baseline TSS of 42/105 (with ≥1 of the allergy symptoms present at a moderate or severe level) during at least 3 or 4 screening days including the morning of randomization, normal ECG, absence of medical conditions that could significantly interfere with the study, and no history of hypersensitivity to antihistamines	Pregnant or lactating women, pts who had received decongestants within 2 days, H1 antagonists (except astemizole) within 7 days, short-acting systemic or topical corticosteroids or intranasal cromolyn within 21d, depot corticosteroids within 2 month or astemizole within 12 wks; pt who had initiated immunotherapy within 1 month of the study initiation or were unable to maintain at a stable dose; pts who currently had an acute respiratory tract infection, otitis media, significant nasal polyps, acute asthma, or have had clinical signs of bacterial sinusitis, and pts who had a significant concomitant illness that might affect the evaluation of the study meds.
Martinez-Cocera 2005 Spain	RCT, ACT, DB, Parallel Multicenter	SAR Pts between 12-65y, diagnosed as suffering SAR caused exclusively by pollen for ≥ 2 yrs and with an acute state of the disease (Nasal symptom score ≥ 5 points_ eligible if they presented a positive skin prick test (diameter of papule >3mm than saline control or ≥10 mg/ml) at inclusion or within 1 yr before inclusion. Women of childbearing potential had to show a negative pregnancy test at study entry and commit themselves to use contraceptive measures during the study.	Pts ineligible who showed: rhinitis due to hypersensitivity to allergens other than pollen (eg, mites) or non-allergenic rhinitis; known hypersensitivity to cetirizine, to compounds structurally related to study drugs or to any other component included; nasal polyps or significant deviation of nasal septum; asthma attack or treatments for asthma in last 3 months; immunotherapy if pts had to receive it during study; treatment with topical antihistamines in previous 48h, nasal decongestants in previous 24h, oral antihistamines (other than astemizole) or disodium cromoglycate in previous 7d, astemizole in previous month, ketotifen in previous 14d, and systemic or topical treatment with corticosteroids (except for topical hydrocortisone <1%), immunosuppressants, or any investigational drug within prior 14d, and pts with out of normal range values in any of these lab blood tests: complete blood count, blood glucose, ironogram, AST, ALT, Total bilirubin, Total protein, urea, creatinine, total cholesterol, and triglycerides.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions
Hampel 2004 USA	Mean age: 37.6y Range: 12-70y 48.6% male Caucasian: 75.3%	L: Loratadine 10 mg qam E1: Ebastine 10 mg qam E2: Ebastine 20 mg qam P: Placebo qam 14-day treatment period	Pts were not permitted to take any other meds for relieving the SAR symptoms nor any meds to another indication that could produce or relieve SAR symptoms. In addition, pts not permitted to take any drug know to increase the Q-T interval corrected for heart rate >444 msec (QTc) or to inhibit CYP3A4 enzyme systems. Steroids were not allowed in any form except as contraceptives.
Martinez-Cocera 2005 Spain	Mean age: 31y Range: 14-65y 49% male Ethnicity: NR	S: satirizing 10 mg po qam R: rupatadine 10 mg po qam 14-day treatment period	No (Pt had to report any concomitant meds that are not listed in exclusion criteria)

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Hampel 2004 USA	Patient-rates symptoms: 0 (absent) to 3 (severe) on pt diary card Patient and physician global evaluation of efficacy: 0 (greatly improved) to 4 (greatly worsened)	80/ 20/ unclear
Martinez-Cocera 2005 Spain	Pts visited at Day -1, Day 7, Day 14 Mean total daily SS: calculated for all study days based on DSS: mean of 2 scores for each day for each symptoms: nasal (runny nose, sneezing, itching, obstruction) and non-nasal (conjunctival itching, tearing, pharyngeal itching); each symptom scored 0-3, 3=severe	37/ 0 / 241

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Hampel 2004 USA	Data given as L vs E1 vs E2 vs P % reduction in scores from baseline: Total score: 33.3 vs 35.9 vs 39.3 vs 28.2 (NSD for E1 and E2 vs L; p<0.05 for E1 and E2 vs P) Total score w/o congestion: 35.3 vs 37.4 vs 41.7 vs 28.7(NSD for E1 and E2 vs L; p<0.05 for E1, E2, and L vs P) Nasal index: 32.2 vs 34.3 vs 38.0 vs 27.7(p<0.05 for E2 vs L; E2 vs P; and E1 vs P) Nasal index w/o congestion: 34.4 vs 34.8 vs 41.1 vs 28.6 (p<0.05 for E2 vs L; E2 vs P; and E1 vs P) Pt global efficacy: % improved, % no change, % worsened 62.1%, 25.9% 12.0% (pts found E2 significantly better than L, p=0.0052) Physician global efficacy rating: % improved, % no change, % worsened 60.0%, 29.0%, 11.0% (NSD compared to P)
Martinez-Cocera 2005 Spain	mean change in TSS: S vs R: -0.65 vs -0.87, NSD Patient global evaluation of efficacy, day 14, S vs R: 75% vs 75.5%, NSD Investigator global evaluation of efficacy, day 14, S vs R: 85% vs 87%, NSD

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Ratner 2004 USA	RCT, DB, placebo- and active-controlled, multicenter	SAR Patients aged 12-70 years with at least 2-year history of fall SAR (nasal congestions, rhinorrhea, sneezing and nasal itch; positive response to skin prick test for ragweed or other fall allergens within 1y; baseline TSS of 42 or 105, with at least one symptom moderate to severe during 3/4 days of screening	History of hypersensitivity to antihistamines; medical conditions that could significantly interfere with the study; pregnancy, lactation, patients who received decongestants within 2d; H1 antagonists (except astemizole) within 7d, astemizole within 12 weeks, steroids or cromolyn within 21d); immunotherapy within 28 days; significant concurrent illness
Saint-Martin 2004 France	RCT, DB, parallel-group, multi-center	SAR Patients aged 12-65 years with SAR due exclusively to pollen for at east 2 years, and with an acute stage of the disease (Nasal SS ≥5), (+) skin prick within last 1y, negative pregnancy test for females in child-bearing years	Non-allergic rhinitis or rhinitis due to hypersensitivity to allergens other than pollens; hypersensitivity to study drugs; nasal polyps or significant nasal septal deviation; acute asthma attach or treatment for asthma in last 3 months; on hyposensitization therapy; treatment with ketotifen in last 2 weeks; any oral antihistamine on cromoglycate during last week; astemizole in last month; topical antihistamines in last 48h; nasal decongestants in last 24h any corticosteroids (except topical hydrocortisone <1%), immunosuppressant, or any investigational drug in last 2 weeks.
van Adelsberg 2003 USA	RCT, DB, parallel-group, multi-center	SAR Non smoking adolescents and adults 15-82 years, symptomatic during the fall, at least a 2-year history of SAR, exceeded a minimum daytime nasal symptom score during placebo run-in period, (+) skin test to local prevalent fall allergen (wheal>=3mm. Patients could have mild asthma	PAR, rhinitis medicamentosa, non allergic rhinitis, structural nasal obstruction, URTI, acute or chronic pulmonary disorder, patients who had begun immunotherapy within the previous 6m Medications not allowed during the study: medications for PAR/SAR and conjunctivitis, medications affecting nasal or ocular symptoms, oral or long-acting inhaled B-agonists, theophylline, leukotriene modifiers

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions
Ratner 2004 USA	Mean age: 38.2y; 90% between 18 and 65y % Female: 61.3 Caucasian: 72%	L: Loratadine 10mg qd E: Ebastine 20mg qd P: Placebo qd Screening period up to 28 days prior to randomization, followed by 28-day treatment period.	Patients were not permitted to take any medication for the purpose of relieving SAR symptoms, centrally acting cardiovascular drugs, antidepressants, any drug that might increase the QT interval, or steroids.
Saint-Martin 2004 France	Mean age: males 32.4y, females 32.9y 4.1% were <18 years old Female: 167/339 Caucasian: 85.8% Basal mTDSS: 1.68	R1: Rupatadine 10 mg qd R2: Rupatadine 20 mg qd L: Loratadine 10 mg qd Duration 2 weeks	None reported; note exclusion criteria
van Adelsberg 2003 USA	Age: 37 years, range 15-82 67% female 82% Caucasian Asthma: 23%	L: Loratadine mg qd M: Montelukast 10 mg qd P: Placebo qd Duration 4 weeks	Short-acting B-agonists for asthma

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Ratner 2004 USA	Patients given daily card and to score their rhinitis symptoms bid. Efficacy assessed by mean SAR symptom scores (0-3 scale, 3=severe); patient and physician global evaluation (0 to 4, with 0=greatly improved, 4=greatly worsened), and study withdrawals due to treatment ineffectiveness. composite score: sum all 5 individual scores; nasal index: sum 4 nasal symptom scores.	41 withdrawn for protocol violation, 15 for treatment failure, 18 for AEs
Saint-Martin 2004 France	All patients received dairy for bid recording of symptoms: rhinorrhea, sneezing, nasal itching, nasal obstruction, conjunctival itching, tearing, and pharyngeal itching; symptoms graded 0-3 (0 absent, 3 severe) Daily symptom score (DSS): mean of bid score for each of 7 symptoms; TDSS: mean of DSS for all 7 symptoms; Mean Total Daily Symptom Score (TDSS): mean of all TDSS values: clinical symptom Score: investigator's assessment of a symptom	65 (19.2%) withdrawn for major protocol deviations; 19 (5.6%) discontinued for other reasons; 255 analyzed
van Adelsberg 2003 USA	Primary endpoint: Daytime nasal symptom score: average of individual symptoms of nasal congestions, rhinorrhea, pruritis, sneezing; recorded in daily diary on awaking Secondary endpoints: Night-time symptoms score: average of individual symptoms of going to sleep, night-time awakenings and nasal congestions on awakening Daytime eye symptoms score: average of tearing, pruritis, redness, and puffiness Each symptom rated 0-3 (0=non, 3=severe) Compositive symptoms score: average of daytime nasal symptoms score, night-time symptoms score	79/NR/1000 Analyzed group had baseline and 1 post-treatment outcomes measured

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Ratner 2004 USA	2-week follow-up: TSS: E<L<P; NSD L vs P, E<L (p=0.0018) Mean % change from baseline: L -24.6, E -32.3, P -23.4 Nasal index: E<L<P (E vs P p<0.05) Individual symptom rhinitis symptom scores E<L or P (p<0.05); most significant differences between L and E were maintained at 4 weeks.
Saint-Martin 2004 France	ITT analysis (patients who took 1+ dose of treatment, n=339): NSD in mTSS among groups; CSS for sneezing and nasal itching was improved in R1 and R2 vs L (p=0.01) Per protocol analysis (completed study, n=255): mTSS R1: 0.8, R2: 0.85, L: 0.92 (p=0.03 among groups), overall efficacy assessment at end of treatment R2>R1>L (p<0.05)
van Adelsberg 2003 USA	L more effective than P for: daytime nasal symptoms score, composite symptoms score daytime eye symptoms score, patient's global evaluation at 2 and 4 weeks; NSD for night-time symptoms L vs M: M had a lower eosinophil count than L; L had a lower daytime nasal symptoms score at 2w than M (p<0.05, data not shown); NSD other comparisons M more effective than P for daytime nasal symptoms score (p=0.003), night-time symptoms score, composite symptoms score daytime eye symptoms score (all p-values 0.006)

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Head-to-head trials			
Ciprandi 1997 Italy	RCT, DB, parallel-group	SAR All pts had a history and diagnosis of allergic rhinoconjunctivitis, w/o asthma, requiring therapy for at least the 2 previous years. All pts were sensitized to a grass and/or Parietaria, as confirmed by skin-prick test, specific IgE and history.	Pregnant, nursing and women with childbearing potential were not eligible for this study, and women were included only if they used appropriate methods of contraception. Pts with upper airway, anatomic nasal problems, or other significant diseases were excluded, as well as pts receiving specific immunotherapy. No medication that would affect the disease were permitted 1 m before and during the study.
Hampel 2003 US	RCT, DB,DD, parallel group, multi-center	SAR Pts were eligible for this study if they were older than 12 y; had a 2 y history of SAR; and exhibited a (+) epicutaneous skin prick test response to grasses, weeds, and/or trees indigenous to the study area during the study period.	Pts were excluded from the study if they lacked a previous response to antihistamines for SAR symptoms; had a history of upper respiratory tract infection; otitis media, or sinusitis within 30 days before the first visit; had undergone treatment with any investigational drugs within 30 d before the first visit; were pregnant or lactating; had received immunotherapy (except those on stable maintenance therapy for at least 6 m before the first visit); or had any serious cardiovascular, hepatic, neurologic, endocrine, or other systemic disease that would make the implementation of the protocol or interpretation of the study results difficult.
Howarth 1999 UK, US, France	RCT, DB, placebo-controlled, parallel-group, multi-center	SAR Pts were eligible to participate in the study if they were 12 to 65 years old, had a history of SAR or at least 2 y, had a (+) skin prick test response to mixed grass pollens (3 mm > (-) control), and provided written consent.	Pts were excluded from entry if they had received intranasal or oral prophylactic therapy that season; had received immunotherapy (unless the immunotherapy had been stable for at least 6 m); had had an upper respiratory tract infection within 30 d before the study; had known serious renal, cardiac, or hepatic disease; were pregnant or lactating; or had received oral or topical H1 receptor antagonists within the last 48 h (with the exception of astemizole, which had to be discontinued for a minimum of 6 w). Pts were also required to meet specific symptom severity criteria.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions
Head-to-head trials			
Ciprandi 1997 Italy	Age: 31 years, range 18-44 38% female	L: loratadine 10 mg qd C: cetirizine 10 mg qd	No medication that would affect the disease were permitted.
Hampel 2003 US	Age: 34.8 years, range 12-70 66% female 67% Caucasian	F: fexofenadine 180 mg qd C: cetirizine 10 mg qd	NR
Howarth 1999 UK, US, France	Age: 33 years 51% male	F1: fexofenadine 120 mg qd F2: fexofenadine 180 mg qd C: cetirizine 10 mg qd P: placebo	NR

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Head-to-head trials		
Ciprandi 1997 Italy	Rhinitis symptoms evaluated by the physician at the visits and recorded daily in the evening on a diary card were; nasal itching and obstruction, sneezing and rhinorrhea using a 4 point scale 0 (absent) to 3 (severe).	0/0/20
Hampel 2003 US	Pts scored symptoms (sneezing, rhinorrhea, itchy nose, palate, or throat; and itchy, watery eyes) based on a 5-pt severity scale (0=symptoms not present, 4=very severe).	16; NR; 479
Howarth 1999 UK, US, France	Symptoms (sneezing; rhinorrhea; itchy nose, palate, or throat; itchy, watery or red eyes; and nasal congestion) were scored in the pt diary on a scale 0 (symptom not present) to 4 (very severe).	22/ NR/ 821 for efficacy; 839 for safety

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Head-to-head trials	
Ciprandi 1997 Italy	TSS: L vs C: -11 (-84.6%) vs -12 (-85.7%); p<0.002. Significant vs baseline NS between groups. Nasal lavage also for inflammatory markers, NS between agents.
Hampel 2003 US	TSS 24 hr overall (95% CI): F vs C: -19.0 % vs -21.6% between treatment -0.22 (-0.59 to 0.15) ; within preset 0.7 margin for 2-sided 95% CI, NSD. A.M. instantaneous: F vs C: -1.27(-1.64 to -0.90) vs -1.44 (-1.83 to -1.06); between treatment –0.18 (-0.55 to 0.20) = equivalent 24 hr reflective, at week 1: F vs C: -1.34 (-1.70 to -0.99) vs -1.56 (-1.93 to -1.19). at week 2: F vs C: -1.84 (CI -2.25 to -1.43) vs -2.09 (-2.52 to -1.66) F vs C overall: - 19.0% -1.56 (-1.92 to 1.20) vs -21.6% -1.78 (-2.15 to -1.40) between treatment -0.22 (-0.59 to 0.15)=equiv. A priori equivalence based on published pediatric results (Pearlman et al 1997) where active agent improved TSS by –1.4, therefore 50% or 0.7 margin was used for total 2-sided 95% CI.
Howarth 1999 UK, US, France	NS between active treatments (mean reduction in 24-hour reflective TSS): F1: -3.0 F2: -3.3 C: -3.3 P: -1.9 (p<0.0001 vs tx)

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Prenner 2000 US	RCT, DB, DD, multi-center	SAR Pts aged 12 to 60 years who had a > 2 year history of SAR (based on self-reporting) were eligible for participation in this study. Pts were required to have hypersensitivity to seasonal allergens prevalent during the study period, as confirmed by a (+) result on a skin test (prick or intradermal). A TSS of >7 (maximum score = 15) was required for entry into the study. All pts were required to be free of clinically significant diseases (e.g., history of hepatic insufficiency, renal failure, uncontrolled asthma, other serious disorders).	Pts were ineligible if they experienced an upper or lower respiratory tract infection within 14 d before visit 1 (screening). Known nonresponders to antihistamines were excluded, as were women who were pregnant or breast-feeding; sexually active women were required to use an acceptable method of birth control if they had not had a hysterectomy or tubal ligation.
Van Cauwenberge 2000 Europe and South Africa	RCT, DB, placebo-controlled, parallel-group, multi-center	SAR For inclusion, all pts had to have a (+) reaction (defined as a weal of > 3 mm in diameter compared to diluent control) to and epicutaneous skin test to grass and/or tree pollen at the screening visit or during the previous 12 m period, as well as a history of responding to antihistamines to relieve allergic symptoms.	Pts were excluded from the study if they had experience an upper respiratory tract infection or sinusitis within the previous 30 d, or had suffered any clinically significant medical or metal disorder that might affect the implementation of the protocol or the interpretation of the resulting data. Further exclusion criteria included: a recent history of drug abuse, females who were pregnant or lactating, and a history of hypersensitivity to any of the investigational treatments. Pts were not allowed to take the following concomitant medications immediately prior to or during the study period: systemic or nasal corticosteroids, nedocromil or cromolyn sodium, oxatomide, oral or nasal decongestants, alpha adrenergic drugs, or other antihistamines. Pts excluded if they had taken any investigational drug within 30 d before the study start.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions
Prenner 2000 US	Age: 35.3 years (fexofenadine), 32.3 years (loratadine) 60% female	L: loratadine 10 mg qd F: fexofenadine 120 mg qd	Concomitant use of other treatments for SAR, including antihistamines, corticosteroids, mast cell stabilizers, decongestants, nasal sprays, eye washes, was prohibited; these medications were appropriately washed out before randomization.
Van Cauwenberge 2000 Europe and South Africa	Age: 31.2 years, range 12-75 55.3% female 90.2% white 1.5% Black 1.8% Asian/Oriental 6.6% Multiracial	L: loratadine 10 mg qd F: fexofenadine 120 mg qd P: placebo	Systemic or nasal corticosteroids, nedocromil or cromolyn sodium, oxatomide, oral or nasal decongestants, alpha adrenergic drugs, or other antihistamines were prohibited.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Prenner 2000 US	Pts and investigator assessed SAR symptoms (nasal discharge, nasal itching, nasal stuffiness, sneezing, and ocular symptoms) using a 4-point scale defined as: 0 (none) to 3 (severe).	NR/ NR/ 659
Van Cauwenberge 2000 Europe and South Africa	Pts had daily symptom diaries; investigators also assessed symptoms at each study visit. Pts also filled out Quality of Life Questionnaire at each visit. At visit 4 (end); pt and investigator assessed efficacy of treatment	46; NR; 639

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Prenner 2000 US	TSS, Patient assessment: L: -39% F: -33% (p=0.019) TSS, Investigator assessment: L: -35% F: -29% (p=0.063)
Van Cauwenberge 2000 Europe and South Africa	NS between active treatments: L: –3.0 (p<0.001 vs placebo) F: –3.3 (p<0.0001 vs placebo) P: –2.1(estimated from Fig 2) Assessment of overall effectiveness, physician assessment: L: 40%; F: 44% P: 36% Patient assessment: L: 42% F: 47% P: 37%

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Internal Validity

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Berger 2003	NR	NR	Yes	Yes	Yes	NR	Yes
Bernstein 2004	Method not reported	Method not reported	Yes	Yes	Yes	Yes	Yes
Bhatia 2005	Unclear, "randomization was assigned by a code in blocks of 4"	NR	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes, study drugs described as identical to placebo
Ciprandi 1997	Yes, method not reported	NR	Yes	Q4. Y	Q5. NR	NR	NR
Ciprandi 2004	Method not reported	NR	No difference on TSS, other characteristics not reported	yes (limited)	NR; study reported as "double blind"	NR; study reported as "double blind"	Assume yes (placebo-controlled)

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Berger 2003	NR	No	Yes	Yes	Manufacturer funded	Fair
Bernstein 2004	Attrition reported (13,6,9% in A,B,C) and adherence (97-99%)	No	No, as attrition 13,6,9% in A,B,C; analysis termed 'ITT" as included all patients who were randomized	None	GlaxoSmithKline Inc., Research Triangle Park, NC	Fair
Bhatia 2005	Attrition 0; others NR	No	Yes; no attrition or exclusions post randomization	None	Study supported by a grant from the investigator sponsored Studies program of AstraZeneca, Westborough, Mass.	Fair
Ciprandi 1997	NR	No	Yes	NR	Manufacturer funded	Fair
Ciprandi 2004	no	NR	unable to determine (states "30 patients were evaluated") but not clear if same as number randomized.	NR	NR	Poor baseline demographic characteristics NR, and randomization and allocation concealment methods NR- may be differences between groups at baseline, also unable to determine number analyzed.

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

External Validity

Author Year	Number screened/ eligible/ enrolled	Run-in/Washout	Class naïve patients only	Control group standard of care	Relevance
Berger 2003	596/NR/440	7 day active run-in with loratadine	No	Yes	
Bernstein 2004	NR/NR/471	7-14d period at baseline designed to assess severity of symptoms. No medications given; no wash-out	NR	NR	Unclear
Bhatia 2005	102/NR/61	None; none	NR	NR	Unclear
Ciprandi 1997	NR/NR/NR	NR	No	Yes	
Ciprandi 2004	NR/NR/30	NR	NR	NR	unclear

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Internal Validity

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Corren 2005	Yes	Yes	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes, study drugs described as identical to placebo
Dockhorn 1987	NR	NR	Yes	Yes	Yes	NR	Yes
Hampel 2003	NR	No	Yes	Yes	Yes	NR	Yes
Hampel 2004	Method not reported	Method not reported	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes; study drugs described as identical to placebo
Horak 2004	Method not reported	Method not reported	NR	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes, study drugs described as identical to placebo
Howarth 1999	NR	NR	Yes	Yes	Yes	NR	Yes

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Corren 2005	Attrition 8/307; others NR	No	No (but only 1 patient with no post baseline data (AZE) not included in analysis)	1 patient in each group was discontinued because of a protocol violation; 4 patients in B and 2 in a discontinued due to AEs	Acknowledgements includes 2 employees of Med Pointe Pharmaceuticals, Somerset, NJ (makers of Astelin®)	Good
Dockhorn 1987	NR	No	Yes	Yes	Manufacturer funded	Fair
Hampel 2003	NR	No, none	Yes	NR	Manufacturer funded	Fair
Hampel 2004	Attrition reported (100/749); others NR	No (100/749=13.3%)	No; attrition=100/749; analyzed all patients who took at least one dose of study medication	Yes: 25 (3.3%) excluded for protocol violation	NR; Aventis Pharmaceuticals, Inc. is the affiliation of one of the investigators	Fair
Horak 2004	Attrition reported (20/120)	No	No; drop-outs 20; some post randomization exclusions, per protocol analysis	Yes: 8 patients excluded for protocol violations, 11 patients excluded as no nasal symptoms at baseline	NR; last author affiliated with Saluc Pharma SA, Prangins, VD (Switzerland)	Poor - not ITT; post-randomization exclusions; NR if groups similar at baseline.
Howarth 1999	NR	No	No	Yes	Manufacturer funded	Fair

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

External Validity

Author Year	Number screened/ eligible/ enrolled	Run-in/Washout	Class naïve patients only	Control group standard of care	Relevance
Corren 2005	398/345/307	Yes; Yes; 1-week, single-blind lead-in period where all allergy medications were discontinued and patients received placebo nasal spray and capsules	NR	NR	Unclear
Dockhorn 1987	NR/NR/330	No	No	Yes	
Hampel 2003	Yes	5-7 day run-in	No	Yes	
Hampel 2004	NR/NR/749	None; none	NR	NR	Unclear
Horak 2004	NR/NR/120	None; none	NR	NR	Unclear
Howarth 1999	1094/NR/842	3-5 day placebo run-in	No	Yes	

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Internal Validity

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Kurowski 2003	Method not reported	Method not reported	Age and sex similar, other characteristics NR	Yes	NR; study reported as "double blind"	Yes, efforts taken to conceal study drug assignment from patients and providers	Yes, efforts taken to conceal study drug assignment from patients and providers
Martinez-Cocera 2005	Yes: computer-generated scheme	Unclear; patients assigned to a sequential randomization number	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes, study drugs described as identical to placebo
Okubo 2004, 2005	Method not reported	Method not reported	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	NR; study reported as "double blind"
Prenner 2000	NR	NR	Yes	Yes	Yes	NR	Yes

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Kurowski 2003	Attrition reported (12 patients did not complete study; others NR; also contamination- one patient took an OTC antihistamine	Yes (12/60=20%)	No; drop-outs 12, including 4 for lack of efficacy and 1 for protocol violation	4 patients discontinued study for aggravation of symptoms: group A 2, B 1, D 1; 1 patient excluded for violation of protocol (took an OTC antihistamine)	Study supported by a grant from medical university of Lodz; study drugs supplied by UCB Pharma, Brussels, Belgium, Schering-Plough, Kenilworth, NJ, and MSD, Whitehouse Station NJ	Poor: high loss to f/u, not ITT, also limited baseline characteristics reported.
Martinez-Cocera 2005	Attrition 37/249; others NR	Yes (15%), but similar rates in both groups	No, as attrition; study termed ITT as primary analysis based on all patients receiving 1+ dose of study drug	Yes; 8 patients received no study medication (no explanation given)	Study partially supported by the National Scientific research program of the Spanish Ministry of Science and Technology	Fair
Okubo 2004, 2005	Attrition reported (3/210 in Okubo 2004, 4 in Okubo 2005); others NR	No (3 or 4 /210)	No; attrition=3 or 4	Yes: 3 did not complete HRQOL questionnaire, 1 received rescue medication (Okubo 2005; note Okubo 2004 states only 3 exclusions)	NR	Fair
Prenner 2000	NR	No	Yes	No	Manufacturer funded	Fair

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

External Validity

Author Year	Number screened/ eligible/ enrolled	Run-in/Washout	Class naïve patients only	Control group standard of care	Relevance
Kurowski 2003	NR/NR/60	None; none	NR	NR	Unclear
Martinez-Cocera 2005	NR/NR/249	None; none	NR	NR	Unclear
Okubo 2004, 2005	250/NR/210	Run-in described in Okubo 2005, but is described as a pre-screening period with no intervention; none	NR	NR	Unclear
Prenner 2000	810/nR/659	Washout before randomization	No	Yes	

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Internal Validity

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ratner 2004	Method not reported	Method not reported	No, C had lower mean years with allergy (p=0.015); NSD for TSS or individual symptom scores at baseline; placebo had fewer mean years with allergy (16 vs 19)	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes
Saint-Martin 2004	Method not reported	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
van Adelsberg 2003	Method not reported	Method not reported	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes, study drugs described as identical to placebo

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Ratner 2004	Attrition or exclusions 12.5%; overall compliance 95.2%	No, 87.5% of 703 completed the study	No- ITT defined as all patients who took at least one dose of study medication; not clear how many did not.	Exclusions for protocol violation [41 patients (5.8%)], treatment failure (15 patients).	NR	Fair
Saint-Martin 2004	Attrition reported; cross-overs, adherence, and contamination NR	Yes: 25% overall withdrawn, 31% in R20 vs 23.2% R10, and 20.7% L10	No, exclusions for protocol violation and patients discontinued for other reasons (total 24.8% lost to follow-up); Reports both ITT and per protocol: 255/347 analyzed per protocol (73.4%)	Yes: 65 patients excluded for major protocol deviations: forbidden treatment, diary cards badly filled, un-allowed range between visits, exclusion criteria, treatment allocation mistake, lack of compliance); yes; 8/347 did not start treatment and were excluded	NR: lead author affiliation Association National de Formation continue en alklergologie, France, and secondary author affiliation: clinical Research Unit, Research Centre, J. Uriach & Cia S.A., Barcelona, Spain	Fair
van Adelsberg 2003	Attrition reported (79/1079); others NR	No	No- ITT defined as all patients who had a baseline and at least one post-treatment assessment.	Patients discontinued the study for adverse clinical experience, laboratory adverse experience, or lack of efficacy A: 5.6% B: 6.3% C: 9.1%	Study supported by a grant from Merck Research Laboratories, Rahway NJ; first author's affiliation is also Merck Research Laboratories	Fair Authors note that study powered for drug-placebo comparisons, not Loratadine to Monolukast

Evidence Table 2. Quality assessment of seasonal allergic rhinitis trials in adults

External Validity

Author Year	Number screened/ eligible/ enrolled	Run-in/Washout	Class naïve patients only	Control group standard of care	Relevance
Ratner 2004	NR/NR/703	no/no	NR	NR	Unclear
Saint-Martin 2004	NR/NR/347	Various drugs excluded for various intervals, see exclusion criteria; no other wash-out. No run-in.	NR	NR	Unclear
van Adelsberg 2003	1728/1177/1079	3-5d single-blind, placebo run-in period; no wash-out	NR	NR	Unclear

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Frolund 1990 Norway	RCT, DB, placebo- and active-controlled, parallel group, multi-center	PAR Pts participating were between the ages of 18-65 years, of either sex with an unequivocal history of perennial allergic rhinitis, and with intermittent or continuous nasal symptoms of at least 1 year. The combined symptom score had to be at least 4.	Excluded from the trial were pts with a history of idiosyncratic reactions to antihistamines or multiple drug allergies or if they had any concurrent disease that would interfere with study results or require treatment, if pregnant, or lactating. Further, pts should not have nasal polyps, deviated septa or any structural defect which might cause nasal obstruction or interfere with clinical evaluation. Pts should not have any ongoing SAR during the study period. Further exclusion criteria: pre-seasonal or co-seasonal immunotherapy with antigen extracts started within 12 m prior to the study, or any maintenance dose of these preparations during the last 12 m before entering the study. Similarly, enrollment was not allowed for pts who had received the following specified type of medication prior to the study start: therapy with loratadine within 3m, systemic or topical corticosteroids, sodium cromoglycate (cromolyn sodium) within 2 wks prior to study, decongestants within 24 h, astemizole within 4 wks, and antihistamines other than astemizole 3 d prior to study. Pts with clinically significant, abnormal laboratory test results were excluded.

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow up/ analyzed
Frolund 1990 Norway	Age range: 18-65 Sex: NR Ethnicity: NR	L: loratadine 10 mg qd C: clemastine 1 mg bid P: placebo	NR	Pts recorded daily nasal (discharge, stuffiness, itching and sneezing) symptom scores 0 (no symptoms) to 3 (severe symptoms), and were to monitor onset of relief in a separate form delivered at visit 1. A new diary card for symptom score recoding during the forthcoming treatment period was distributed to the pts at each visit. Rhinoscopy was made at each visit to assess nasal membranes, secretion and patency (0=normal, 3=abnormal).	25/NR/130

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
Frolund 1990 Norway	TSS 1 weeks: L significantly better than C (p<0.05, *estimated from figure) L vs C vs P: -49% vs -31% vs -10% TSS 2 weeks / 3 weeks: NSD between active treatments, significant vs. P (p<0.05 *estimated from figure at 2/3 weeks) L vs C vs P: - 61% / 53% vs -40% / 44% vs -8% / 10% Nasal symptom scores: L significantly better than C at 1 week for nasal itching, stuffiness, p <0.05 (concurred w/ patient diaries); NSD at 2 or 3 weeks. Active treatment significant vs P, p<0.01. Eye symptoms scores: NSD between active treatments. Active treatments significantly better than P for itching/redness p<0.05, NS for tearing. Rhinoscopy: Active treatments significantly better vs. P, p<0.05 Onset: L significant vs. C at day , p<0.05. * Diary responses not individually reported

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Simons 2003 US and Canada	RCT, DB, placebo-controlled, parallel group, multi-center	Age 12 years or older, history of moderate PAR symptoms of at least 2 years' duration, and had a positive skin test response to 1 or more allergens (house dust mite, cockroach, mold, an animal dander) within the previous 12 months. At the screening visit, they were required to have PAR symptoms with a 12-hour reflecive TSS, including nasal stuffiness-congestion, of at least 10 (maximum score 24) and no greater than moderate nasal stuffiness/congestion. Summed reflective score for congestion during 3 days before baseline was required to be at least 60; overall rhinitis score at baseline was required to be greater than 2 (on a 4-point scale), indicating moderate-to-severe disease. Good general health as confirmed by history, physical exam, hematology, and blood chemistry test, and urinalysis. Women of childbearing potential required to have a negative serum pregnancy test at screening and to use a medically accepted method of contraception before screening and during the study.	SAR triggered by an allergen pollinating during the time of the study, structural abnormalities interfering with nasal airflow, upper respiratory tract or sinus infection requiring antibiotic treatment withn 14 days before screening, a viral upper respiratory tract infection during the 7 days before screening, and current or past history of recurrent or chronic sinusitis, chronic purulent postnasal drip, rhinitis medicamentosa, or asthma that necessitated the regular use of inhaled corticosteroids or use of systemic corticosteroids. Also excluded were patients with a history of adverse reactions to more than 2 classes of medications or those with a history of adverse effects to antihistamines. Patients who had used any investigational drug in the 30 days before screening, as well as those judged to be dependent on decongestants (nasal, oral, or ocular), intranasal H-1 antihistamines, or intranasal corticosteroids, were also excluded. Patients receiving allergen immunotherapy excluded unless they were on a regular maintenance schedule before screening and could maintain this schedule for the d desensitization treatment within 24 hours before a study visit was prohibited. Preg

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Age Gender Ethnicity	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow up/ analyzed
Simons 2003 US and Canada	34.8 (range 11-79) 70.6% women 82.0% white, 6.4% black, 1.6% Asian, 9.2% Hispanic, <1% other	D: desloratadine 5 mg qd P: placebo 4 weeks	Pseudoephedrine permitted as needed for treatment of severe nasal congestion	Symptom scores recorded on daily diary cards. Symptoms (I.e., rhinorrhea, nasal itching, sneezing, postnasal drip/drainage, itchy/burning eyes, tearing/watering eyes, and itching of ears or palate) were individually assessed on a 4-point scale (0=none, 3=severe). TSS was the sum of the 4 nasal symptoms and 3 non nasal symptoms. Congestion not included in TSS because patients could use pseudoephedrine as needed. Participants scored severity of PAR twice daily on basis of previous 12 hours (reflective) and at the time of assessment (instantaneous). Overall severity assessed jointly by investigators and participants at baseline at subsequent visits using a 4-point scale (0=none, 3=severe). Overall response also assessed jointly by investigators and participants at each post baseline visit on a 5-point scale (1=complete relief, 5=treatment failure)	42/NR/NR (676 enrolled)

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
Simons 2003 US and Canada	Change from baseline in mean instantaneous TSS (excluding nasal symptoms) D: –35.0% P: –27.4% (p=0.005) Change from baseline in mean instantaneous TSS (including nasal symptoms) D: –30.8% P: –23.8% (p=0.006) Change from baseline in mean reflective TSS (excluding nasal symptoms) D: –37.9% P: –32.3% (p=0.007)

Evidence Table 4. Quality assessment of perennial allergic rhinitis trials in adults

Author Year	*Internal Validity* Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination
Frolund 1990	Yes, computer generated code	NR	Yes	Yes	NR	NR, same assessor each time	Yes, identical capsules all twice daily	NR
Simons 2003	Yes, computer generated code	NR	Yes	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Attrition yes, others no.

Evidence Table 4. Quality assessment of perennial allergic rhinitis trials in adults

						External Validity			
Author Year	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Funding**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**
Frolund 1990	Yes, 16%	Appears yes for AEs	NR	Manufacturer funded	Fair	NR	No	No	Yes
Simons 2003	No	Unable to determine, number analyzed not reported	NR	Schering-Plough	Fair	NR/NR/676	none reported	NR	Yes

Evidence Table 4. Quality assessment of perennial allergic rhinitis trials in adults

Author Year	Comment
Frolund 1990	Quality rating-patient diary responses reported in figures without individual values
Simons 2003	

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Seasonal allergic rhinitis		
Day et al., 1997 (Fair)	Double-blind, single-center, Environmental Exposure Unit	Age 14 to 70 with a documented clinical history of SAR for the previous 2 years and positive epicutaneous skin tests to ragweed antigen. Women allowed to participate if they were not pregnant or lactating and were using a medically prescribed method of birth control before entering the study. Positive responders to pre-study priming exposure in the Environmental Exposure Unit, defined as two or more of the following symptoms rated as moderate or severe after pollen exposure for 60 minutes: sneezing, rhinorrhea, itchy nose/palate/throat; itchy/watery/red eyes.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Seasonal allergic rhinitis	
Day et al., 1997 (Fair)	Any symptom rated as "very severe" (I.e., so severe as to warrant the use of agents other than antihistamines) on the day of the entry visit; a current URTI; evidence of current sinusitis; malnutrition, blood dyscrasia, renal or hepatic insufficiency, chronic infection, drug abuse, or alcoholism, malignancy, or malabsorption; clinically significant hepatic, neurologic, endocrine, or other major systemic disease making implementation or interpretation of the protocol results difficult; possessed a mental capacity limited to the extent that the subject cold not provide legal consent or understand information regarding side effects or tolerance of the drug; any disease state or surgery known to affect the GI absorpton of drugs; a history of prolonged QT intervals or conditions(s) that may lead to QT prolongation; were receiving desensitization therapy in changing doses within 30 days of the entry visit (subjects on maintenance immunotherapy were acceptable); used: systemic oral corticosteroids (within 90 days of the entry visit); systemic injectable corticosteroids (90 days); intranasal or inhaled corticosteroids, systemic antibiotics for respiratory infections, or topical cromolyn sodium (2 weeks); investigational drug (30 days); astemizole (3 months); ketoconazole or fluconazole (3 months); hydroxyzine (72 hours); macrolide ntibiotics (7 days); a hypersensitivity to antihistamines or their tablet ingredients; could not discontinue use of corticosteroied or any substance having antihistamine properties (e.g., phenothiazine, tricyclic antidepressants), anticholinergic, sedatives, hypnotics, adrenergic drugs, cromolyn sodium, antihistamines; ketoconazole or fluconazole, or macrolide antibiotics.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Seasonal allergic rhinitis					
Day et al., 1997 (Fair)	30.6 44.3% male NR	T: terfenadine 60 mg C: cetirizine 10 mg, L: loratadine 10 mg A: astemizole 10 mg P: placebo Single dose	Primary outcome: Time to onset of clinically important relief from SAR symptoms. Defined as "marked relief" or "complete relief" of symptoms documented at 3 consecutive time points on the effectiveness scale. "Time to onset" was defined as the first time point of the 3 consecutive time points. Included in this objective was an analysis of the number of subjects in each treatment group who achieved clinically important relief of symptoms Secondary outcomes:	NR/115/111	NR/NR/55 analyzed for primary outcome ('responders')

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Seasonal allergic rhinitis	
Day et al., 1997 (Fair)	Relief of clinically important symptoms (%): T: 54.5% C: 69.6% L: 50.0% A: 40.9% P: 31.8% p=0.119 for ANOVA cetirizine vs placebo p=0.025; other pairwise comparisons NS Time to onset of clinically important relief (hours:minutes): T: 2:20; 2:14 C: 1:45; 1:47 L: 2:28; 2:16 A: 2:16; 1:54 O: 2:35; 2:41 p-value for median, based on survival curves=0.032

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Day et al., 1998 (Fair)	Double-blind, single-center, Environmental Exposure Unit	Men and women age 16 or older, with a history and diagnosis of SAR caused by ragweed pollen and serious enough to require pharmacologic treatment each year for at least 2 years. Prevalent season allergy had to have been documented by a recognized skin prick test of at least moderate reaction at Phase I or within the past year.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Day et al., 1998 (Fair)	Serious diseases, significant disorders of the major organs systems, or other abnormalities except those related to underlying allergic rhinitis. Clinically significant naal anatomic deformities causing more than 50% obstruction (e.g., septal defects and polyps) and those who had experienced a recent episode of acute sinusitis or acute respiratory infection (including the common cold); patients treated with chronic asthma medication, except beta agonist inhalers used in conjunction with exercise; patients initiating or advancing immunotherapy during the course of the study or used H1-receptor antagonists, decongestants or saline nasal sprays; allergic ophthalmic treatments; inhaled and/or topical corticosteroids; intranasal or optical cromolyn; nonoamine oxidase inhibitors; reserpine; beta blockers; systemic corticosteroids; or astemizole within prespecified relevant periods or time. Intolerance to antihistamines, had used an investigational drug within 1 month of the study, or had participated in a previous cetirizine study. Women were either not pregnant as verified by serum pregnancy test, not of child-bearing potential, or using approved methods of contraception. Nursing mothers excluded.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Day et al., 1998 (Fair)	31.4 42.6% male 93.1% white, <1% black, 3.0% Asian, 1.0% Hispanic, 2.0% other	C: cetirizine 10 mg L: loratadine 10 mg P: placebo 2 days	Patients rated symptoms every half hour in diaries provided in the EEU. Symptoms excluding nose blows, sneezes, and stuffiness (0=none, no symptoms whatsoever to 5=very severe, bothersome and disabling). An 8-point scale used to measure severity of nose blows and sneezes. Stuffy nose (0=clear, to 4=blocked) Global satisfaction with treatment (1=excellent, 5=poor) Personal satisfaction with treatment (1=exceptionally satisfied, 5=unsatisfied)	304/202/202	8/NR/202

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Day et al., 1998 (Fair)	Overall mean % reduction in Total Symptom Complex: C: 36.7% ($p \leq 0.01$ vs loratadine and vs placebo) L: 15.4% (NS vs placebo) P: 12.0% Overall mean % reduction in Major Symptom Complex: C: 37.4% ($p < 0.01$ vs loratadine and vs placebo) L: 14.7% (NS vs placebo) P: 6.7% Onset of action C: significant reduction in TSC severity vs placebo evident 1 hour after 1st dose ($p \leq 0.02$) L: onset of action in TSC evident by hour 3 ($p \leq 0.02$) (Results for MSC similar to TSC results) Global assessment of efficacy (% satisfied patients) C: 60.9% L: 50.0% P: 43.1% (NSD) Personal satisfaction with therapy (% satisfied) C: 64.1% (p vs P =0.04; p-value vs L NR) L: 45.5% P: 41.5%

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose) (Fair)	Double-blind, single-center, Environmental Exposure Unit	Outpatients age 16 or older, men and women either not of childbearing potential or agreeing not to become pregnant and using defined effective methods of contraception; documented SAR severe enough to require pharmacologic treatment for the past 2 consecutive years; diagnosis confirmed by skin-prick test to ragweed antigen at or within 1 year of screening.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose) (Fair)	Known allergies to study medications or excipients; clinically significant nasal anatomic deformities causing >50% obstruction ; acute or chronic sinusitis, otitis media, or URTI (including coryza) within 30 days of priming; asthma requiring medication beyond occasional use of inhaled short-acting beta-agonists; subjects could not be initiating or advancing immunotherapy or using corticosteroids, leukotriene modifiers/antagonists, cromolyn, iprratropium bormide, monoamine oxidase inhibitors, reserpine, beta-blockers, astemizole, norastemizole, monoclonal anti-immunoglobulin E antibody, or other miscellaneous antiallergy/decongestant treatments within prespecified periods; taking agents with a potential for interactions with study medication or potential effects on symptoms; those who had recently donated blood or participated in other studies. Subjects required to be free of other predefined illnesses or disorders, which in the judgment of the investigator were determined to be clinically significant and/or alter the subject's ability to participate in the clinical trial.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose) (Fair)	40.0 44.3% male 94.4% white, 2.1% black, 2.1% Asian, 1.4% other	C: cetirizine 10 mg F: fexofenadine 180 mg P: placebo 2 days	Patient self report. Symptoms (runny nose, sneezing, itchy nose/palate/throat, itchy/watery eyes, and stuffy nose) individually self-rated (0=absent, 1=mild, 2=moderate, 3=severe) at 30-minute intervals in phase II, 20-minute intervals in phase III. Global evaluation of effectiveness (1=major improvement, 7=severe worsening) at conclusion of final treatment day. Personal satisfaction with treatment (1=very satisfied, 5=very unsatisfied) Willingness to take study medication again for SAR (1=definitely would, 5=definitely would not)	836/575/575	13/NR/574

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose) (Fair)	Change from baseline in mean TSSC score 21 to 24 hours after first dose: C: -3.6 (p<0.001 vs fexofenadine; <0.001 vs placebo) F: -2.7 P: -2.0 Patients on cetirizine had a 33% greater reduction in TSSC than those on fexofenadine. For subjects' global evaluation of effectiveness, satisfaction with treatment, and willingness to take study medication, both treatment groups were better than placebo (data not reported). For pairwise comparisons, "Differences numerically favored cetirizine but did not reach statistical significance " (data not reported) Change from baseline in mean TSSC score 12 hours postdose: C: -4.3 (p<0.001 vs fexofenadine, <0.001 vs placebo) F: -3.4 (p<0.001 vs placebo) P: -1.9 Average change in TSSC over 5 to 12 hours postdose: C: -5.0 (p=0.006 vs F, <0.001 vs P) F: -4.4 (p<0.001 vs P) P: -2.3 Differences between active treatments were observed beginning at 5.5 hours postdose. C associated with significantly greater reductions in TSSC scores than F at 11 of 15 times points within the 5- to 12-hour postdose period (p<0.05 to ≤0.001)

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Horak et al., 2005 (Fair)	Double-blind, outdoor parks during spring allergy season in San Diego and Iowa City	Male and female, age 12 years or older, with a history of SAR for at least 2 years and who were confirmed within the previous year to be sensitive to an allergen prevalent at the time of the study according to a recognized skin test. All patients underwent physical examinations and were required to be free of major diseases. Women were either not of childbearing potential or agreed to use acceptable methods of birth control to avoid pregnancy, had a negative pregnancy test result at the time of the screening visit, and were not nursing mothers.
Hyo et al., 2005 (Poor)	Double-blind, outdoor park during Japanese cedar pollen season	Moderate or worse nasal symptoms of SAR between February and April 2002 and Japanese cedar specific IgE.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Horak et al., 2005 (Fair)	Significant nasal anatomic deformities causing more than 50% obstruction and those who had experienced an episode of acute sinusitis within 30 days of the study; patients who had used medications to treat allergies or other chronic or acute upper respiratory tract disease at intervals predetermined to be unacceptable.
Hyo et al., 2005 (Poor)	Upper respiratory tract infections and sinusitis.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Horak et al., 2005 (Fair)	25.8 (SD 4.5) 40.4% male Race/ethnicity NR	F: fexofenadine 120 mg L: levocetirizine 5 mg P: placebo Single dose	Primary outcome: Patient self-report, change from baseline in Major Symptoms Complex Score (MSCS=sum of rhinorrhea, sneezing, itchy nose, and itchy eyes) during time interval 2 (22 to 24 hours after drug intake). Major secondary variables: change from baseline in MSCS and the individual symptoms during all time intervals; difference from baseline in the subject's global evaluation of satisfaction; subject's readiness to use the same medication in the future.	NR/NR/94	10/NR/Not clear
Hyo et al., 2005 (Poor)	33.8 62.7% male Race/ethnicity NR	C: cetirizine 10 mg F: fexofenadine 120 mg L: loratadine 10 mg P: placebo 2 days	Patient self report. Number of paroxysmal sneezes and nose blows recorded, nasal congestion, nasal itching, eye itching, and watering of the eyes (0=none to 10=very severe). Quality of life surveyed with JRQLQ (0 to 4, higher=poorer QOL)	NR/NR/NR	7/NR/83

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Horak et al., 2005 (Fair)	Mean change from baseline to 22-24 hours after drug intake in MSCS: F: -3.84 (p<0.001 vs placebo) L: -5.10 (p< 0.001 vs fexofenadine and vs placebo) P: -1.87 Both active treatments improved symptoms within the first 2 hours. Global evaluation of satisfaction: During first 2 hours after medication intake, slight improvement of satisfaction over baseline, with NSD between active treatments. During all assessment periods on day 2, L significantly better than F in improving satisfaction. Subjects ready to use same treatment in the future: L: two-thirds F: half P: one-quarter (data, p-values not reported)
Hyo et al., 2005 (Poor)	Reduction from baseline in Total Symptom Scores 1 to 3 hours after administration: C: 45% to 48% on both days (p=0.04 vs F and L; p=0.006 vs P) F: 42% to 48% on day 1; reduction on day 2 lower (p=0.04 vs P) L: 30% to 40% on day 2 (NSD vs P) Changes from baseline in QOL scores: C: 24.7% F: 19.3% L: 33.2% P: -12.9% NSD among 3 active treatment groups; all active treatments were significantly improved vs P

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Meltzer et al., 1996 (Fair)	Double-blind, outdoor parks in spring allergy season in San Diego and Iowa City	Male and female, age 12 years or older, with a history of SAR for at least 2 years and confirmed within the previous year to be sensitive to an allergen prevalent at the time of the study according to a recognized skin test; all underwent a physical exam at the time of screening and were required to be free of major diseases. Women were either not of childbearing potential or agreed to use acceptable methods of birth control to avoid pregnancy, had a negative pregnancy test result at the time of he screening visit, and were not nursing mothers.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Meltzer et al., 1996 (Fair)	Patients with significant nasal anatomic deformities causing more than 50% obstruction and those who had experienced an episode of acute sinusitis within 30 days of the study. Patients who had used medications to treat allergies or other chronic or acute upper respiratory tract disease at intervals predetermined to be unacceptable.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Meltzer et al., 1996 (Fair)	28.8 (range 13-62) 50% male 86% white, 5% black, 9% other	C: cetirizine 10 mg L: loratadine 10 mg P: placebo 2 days	Patient self-report (diary card); collected in park after each assessment; diary cards completed at home on day 1 were collected at the beginning of the second day.` Primary endpoint: major symptom complex (MSC; composite of runny nose, sniffles, itchy nose, nose blows, sneezes, and watery eyes) and total symptom complex (TSC, MSC plus itchy eyes or ears, itchy throat, cough, and postnasal drip) severity scores. Global efficacy of treatment rated at end of study or at discontinuation (1=excellent, 5=poor) Personal satisfaction with treatment (1=exceptionally satisfied, 5=unsatisfied)	316/279/279	4/2/278

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Meltzer et al., 1996 (Fair)	Reduction from baseline in **MSC** (1st number) severity scores; and **TSC** (second number) severity scores (overall) C: 5.9 ; 9.4 (p<0.01 vs L and vs P) L: 4.4; 7.3 P: 4.4; 7.5 Reduction from baseline in **MSC** (1st number)severity scores; and **TSC** (second number) severity scores (first 24 hours) C: 4.1; 6.3 (p<0.01 vs L and vs P) L: 2.3; 3.8 P: 2.6; 4.7 Reduction from baseline in **MSC** (1st number)severity scores; and **TSC** (second number) severity scores (last period) C: 7.5; 11.9 (p<0.05 vs L and vs P) L: 6.2; 10.1 P: 6.3; 10.3 Patient assessment of global efficacy C: 73.6% improved, 22.0% fair, 4% poor L: 56.5% improved, 33.7% fair, 9.8% poor (p=0.05 vs C) P: 59.3% improved, 29.7% fair, 12.0% poor (p=0.08 vs C) Patient appraisal of personal satisfaction with treatment C: 65.9% satisfied, 23.1% neutral, 11.0% unsatisfied L: 60.9% satisfied, 27.1% neutral, 12.0% unsatisfied (p=0.77 vs C) P: 61.5% satisfied, 28.6% neutral, 9.9% unsatisfied (p=0.70 vs C)

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Satish et al., 2004 (Fair to Poor)	Double-blind, crossover, performance simulation	Adults who had SAR for at least two consecutive years, recruited with the assistance of physicians specializing in allergy and immunology; between ages 18 and 60 years, skin test positive (prick or intradermal) to a seasonal allergen, which included seasonal molds, prevalent during the study period; have a negative urine screen test for drugs with abuse potential, be free of clinically significant disease (other than SAR) and free of drug treatment that could impact performance.
Weiler et al., 2000 (Fair)	Double-blind, crossover; driving simulator	Ability to remain for 5 hours after drives, history of alcohol use and willingness to consume alcohol; age 25 to 45 years, SAR caused by ragweed pollen, previous successful use of antihistamines to treat SAR, status as a currently licensed experienced driver who drove an average of at least three times a week for at least 3 years, and 20/20 corrected vision.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Satish et al., 2004 (Fair to Poor)	Alcohol abuse or consumed alcohol in more than minimal amounts; either tested negative for asthma or had symptoms under control by use of a beta agonist. Pregnant and nursing women excluded.
Weiler et al., 2000 (Fair)	Medical conditions that might interfere with ability to perform the study, pregnancy or lactation, unusual sleep pattern (including those of third-shift workers), excessive alcohol consumption, use of tobacco in the past year or excessive caffeine consumption, previous experience in the Iowa Driving Simulator, and a positive result on a drug screening test.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Satish et al., 2004 (Fair to Poor)	Median age 37 (range 18-48) 52% male 96% Caucasian	D: desloratadine 5 mg P: placebo 3 doses (morning and evening on the day prior to research participation, and following morning on the day of participation)	Strategic management simulation performance measures of decision making, baseline and after the third dose of medication.	NR/NR/48	Not clear (states "44 patients completed the study")
Weiler et al., 2000 (Fair)	31 (range 25-44) 37.5% male 92.5% white	F: fexofenadine 60 mg D: diphenhydramine 50 mg P: placebo (with or without alcohol) single dose	Data on driving performance measures using Iowa Driving Simulator; 4 sessions one week apart.	71/NR/41	1/0/40

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Satish et al., 2004 (Fair to Poor)	During allergy season, performance on 6 of 9 categories (Task Orientation, Applied Initiative, Information Orientation, Basic Activity Level, Breadth of Approach, and Strategic Complexity) categories showed lower performance levels during P treatment than during desloratadine treatment ($p<0.05$). In categories of Task Orientation, Applied Initiative, and Information Orientation, D treatment of previously symptomatic individuals was not significantly different from performance levels that were measured at baseline (when participants were asymptomatic for SAR outside the allergy season). Speed of Response, Emergency Responsiveness, and Planning Distance showed no overall significant differences. Patient-rated symptom severity, both for nasal and non-nasal symptoms of rhinitis, was greater when patients were treated with P than D (data NR)
Weiler et al., 2000 (Fair)	Coherence (ability to maintain a constant distance from a lead car that varied its speed randomly): Less coherence with D than with alcohol, F or P. Minimum following distance: Worse performance with alcohol (15.1 m) than with F (17.1 m) or P (17.4 m) Steering instability: Better performance with fexofenadine than with D or alcohol (but not P). Lane excursions NSD between 4 treatments for excursions to the right. For excursions to the left, worse performance with D than with F or P. NSD between F and P. . Response to blocking vehicle: NSD between treatments for speed of response. Subjective drowsiness ratings NSD between treatment groups 1 hour after capsule administration. At measures of drowsiness before and after drives, participants most drowsy after taking D and least drowsy after taking F or P.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Perennial allergic rhinitis		
Lee et al., 2004 (Poor)	Double-blind, crossover	History of PAR, required to exhibit a positive reaction to house dust mite on skin prick testing; required to demonstrate a positive response to nasal adenosine monophosphate (AMP) challenge at initial screening as defined by a maximal fall in peak nasal inspiratory flow of at least 20% from baseline.
Allergic rhinitis, not specified		
Passalacqua et al., 2004 (Fair)	Double-blind, crossover.	Adult outpatients, age 15-65 years, referred to one clinic for respiratory allergy; had to have suffered from intermittent AR fro at least 2 years. Allergic etiology was established by means of skin tests, performed with a standard panel of geographically relevant allergens: house dust mites, grasses, Parietaria, birch, olive, hazelnut, cat dander, dog dander, and Alternaria tenuis. Skin sensitivity to at least one of the mentioned allergens was required. Patients had to be medication-free and symptomatic at the time of enrollment and before receiving the other drug.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Perennial allergic rhinitis	
Lee et al., 2004 (Poor)	Course of oral corticosteroids or antibiotics for at least 3 months.
Allergic rhinitis, not speci	
Passalacqua et al., 2004 (Fair)	Not reported

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Perennial allergic rhinitis					
Lee et al., 2004 (Poor)	43 (SD 3) 43.8% male Race/ethnicity NR	F: fexofenadine 180mg B: butterbur 100 mg P: placebo 1 week	Patient self-report (diary card). Nasal symptom score (0=no symptoms, 3=severe symptoms) for runny nose, stuffy nose, itchy nose, and sneezing. Total score (out of 12) calculated and average of last 5 days of each randomized treatment used for analysis. Measured in response to adenosine monophosphate challenge	NR/NR/16	NR/NR/16
Allergic rhinitis, not speci					
Passalacqua et al., 2004 (Fair)	36.7 (range 18-57) 39.1% male Race/ethnicity NR	D: desloratadine 5 mg L: levocetirizine 5 mg Single dose	Patient self-report reflective TSS= sum of nasal symptoms (sneezing, itching, rhinorrhea, obstruction and ocular redness/itching; 0=absent, 3=severe) at baseline and 24 hours after administration of drug instant TSS=symptoms at 20 minutes, 40 minutes, and 1, 2, 4, 6, 8, 12 hours after drug administration.	NR/NR/23	NR/NR/23

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Perennial allergic rhinitis	
Lee et al., 2004 (Poor)	Change from baseline in nasal symptom score: F: 1.8 (± 0.4) B: 1.8 (± 0.4) P: 2.8 (± 0.5) p<0.05 vs P for both F and B; between-group p-value NR
Allergic rhinitis, not speci	
Passalacqua et al., 2004 (Fair)	Change in reflective TSS (baseline and 24h measures) D: 11.3 ± 2.5 vs 7.9 ± 2.4 (p<0.05) L: 11.53 ± 2.2 vs 8.0 ± 2.0 (p<0.05) Change in nasal obstruction score alone (baseline and 24h measure): D: 2.0 + 0.3 vs 1.1 + 0.3 (p<0.05) L: 1.9 + 0.4 vs 1.2 + 0.2 (p<0.05) No differences between treatments Scores for instant TSS and obstruction score alone, evaluated at the scheduled time points, progressively decreased with both drugs in parallel. 2 hours after dosing, instant TSS score was significantly lower with L than D No difference between drugs at any time for obstruction.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Study Design Setting	Eligibility criteria
Simons et al. 2000 (Fair)	RCT, double-blind, crossover, single-dose, single-center.	Light-skinned, age 6 to 11 years, non-obese, non-smokers, in good health except for allergic rhinitis with or without mild asthma.

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Exclusion criteria
Simons et al. 2000 (Fair)	NR

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Mean Age Gender Race/ethnicity	Interventions (drug, dose duration)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Simons et al. 2000 (Fair)	9 (SEM 0.4) years 87% male Race/ethnicity not reported	C: cetirizine 10 mg L: loratadine 10 mg P: placebo Single dose	Skin tests performed before medication or placebo administration at around 0800 h, at 15 minute intervals during the first hour afterwards, at hourly intervals thereafter for 7 hours, and at 24 hours. Each time skin tests were performed, children asked to assess amount of itching as absent, present and mild, or present and severe	NR/NR/15	0/0/15

Evidence Table 5. Allergic rhinitis trials in adults with less than 14 days' followup

Author, year (Quality score)	Results
Simons et al. 2000 (Fair)	Suppression of wheals and flares compared with baseline C: Significant suppression of wheals from 0.25 to 24 hours, with a maximum of 49% at 7 hours, and significant suppression of the flares from 0.5 to 24 hours, with nearly 100% suppression from 2 to 24 hours, inclusive. L: Significant suppression of wheals from 0.75 to 24 hours, with a maximum of 46% suppression at 7 hours, and significant suppression of the flares from 0.75 to 24 hours, inclusive, with a maximum of 90% suppression at 4 hours. P: Significant suppression of wheals from 0.25 to 2 hours and from 4 to 7 hours, and significant suppression of the flares from 0.5 to 1 hour. C suppressed wheals significantly more than L from 0.25 to 1 hour inclusive, and suppressed flares significantly more than L at 0.5, 1, 2, 3, 5, 6, 7, and 24 hours. In 9 children who experience itching of wheals and flares at baseline: C: Completely suppressed itching from 0.75 to 7 hours, inclusive L: Completely suppressed itching at 3 and 5 hours P: Did not completely suppress itching at any time

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

Internal Validity

Author Year Country Trial Name (Quality Score)	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Day et al., 1997	Method NR	NR	Yes	Yes	Unclear, reported as double blind	Not specified (study described as double-	Yes
Day et al., 1998	Yes	NR	Yes	Yes	Unclear, reported as double blind	Not specified (study described as double-blind)	Yes
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose)	Method NR	NR	Yes	Yes	Unclear, reported as double blind	Not specified (study described as double-blind)	Yes
Horak et al., 2005	Method NR	NR	NR (crossover, does not report characteristics by order of randomization)	Yes	Unclear, reported as double blind	Not specified (study described as double-blind)	Yes

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

Author Year Country Trial Name (Quality Score)	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Day et al., 1997	Attrition and contamination yes, others no	No	Yes for primary outcome; time to onset reported only for responders (55/111)	No	Nordic Merrell Dow, Quebec	Fair
Day et al., 1998	Yes, no, no, no	No	Not clear, states that ITT analysis was conducted, but not defined.	No	Pfizer	Fair
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose)	Yes, no, no, no	No	574/575 analyzed	Yes (1 of 575, capsule lodged in throat, withdrew)	Pfizer	Fair
Horak et al., 2005	Attrition yes, others no	No	Not clear. ITT defined as all randomized subjects who received at least one dose of study medication, but number analyzed not specified. 84/94 completed; but no information on reasons for attrition	NR	UCB Farchim, Bulle, Switzerland	Fair

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

External Validity

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/ enrolled	Run-in/Washout	Class naïve patients only
Day et al., 1997	NR/115/111	No	NR
Day et al., 1998	304/202/202	No	NR
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose)	836/575/575	No	NR
Horak et al., 2005	NR/NR/94	At least 12-day washout between drugs	NR

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

Internal Validity

Author Year Country Trial Name (Quality Score)	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Hyo et al., 2005	Method NR	NR	Yes	Yes	Unclear, reported as double blind	Not specified (study described as double-blind)	Yes (placebo)
Lee et al., 2004	Method NR	NR	NR (crossover, does not report characteristics by order of randomization)	Yes	Unclear, reported as double blind	Not specified (study described as double-blind)	Yes
Meltzer et al., 1996	Method NR	NR	No statistical analysis, appear similar	Yes	Unclear, reported as double blind	Not specified (study described as double-blind)	Yes (placebo, double-dummy)

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

Author Year Country Trial Name (Quality Score)	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Hyo et al., 2005	Attrition yes, others no	No (93.8% analyzed)	Number analyzed NR. 7/113 (6.2%) subjects did not participate on study day.	Yes (7/113 excluded for sickness on study days)	NR	Poor: Analysis not ITT, attrition by group NR, baseline differences in symptoms and methods of randomization and allocation concealment NR.
Lee et al., 2004	No	Unable to determine	Unable to determine (states, "16 patients were enrolled and all completed the study per protocol," but no definition of per protocol)	Unable to determine	University of Dundee departmental grant, no funding from pharmaceutical industry.	Poor: No data on baseline differences between groups (by order of administration); unable to determine number randomized.
Meltzer et al., 1996	Attrition and adherence yes.	No	278 of 279 analyzed	1 of 279 (placebo group, for noncompliance)	Pfizer	Fair

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

	External Validity		
Author Year Country Trial Name (Quality Score)	**Number screened/ eligible/ enrolled**	**Run-in/Washout**	**Class naïve patients only**
Hyo et al., 2005	NR/NR/113	No	NR
Lee et al., 2004	NR/NR/16	1-week washout between treatments.	NR
Meltzer et al., 1996	316/279/279	No	NR

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

Internal Validity

Author Year Country Trial Name (Quality Score)	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Passalacqua et al., 2004	Yes	NR	NR (crossover, does not report characteristics by order of randomization)	Yes	Yes	Yes	Yes
Satish et al., 2004	Method NR	NR	NR (crossover, does not report characteristics by order of randomization)	Yes	Not specified (study described as double-blind)	Not specified (study described as double-blind)	Yes (placebo)
Simons et al., 2000	Yes	NR	NR (crossover, does not report characteristics by	Yes	Not specified (study described as double-blind)	Not specified (study	Yes (placebo)
Weiler et al., 2000	Method NR	NR	NR (crossover, does not report characteristics by order of randomization)	Yes	Yes	Likely ("both researchers and participants were blinded to treatment.")	Yes

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

Author Year Country Trial Name (Quality Score)	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Passalacqua et al., 2004	No	NR	Unclear; number analyzed NR.	NR	Associazione Ricerca Malattie Immunologiche e Allergiche.	Fair
Satish et al., 2004	Attrition and contamination yes, others no	Not high, 4 of 48 did not complete, groups not specified.	No. 44 of 48 analyzed.	Yes (1 patient used drugs that were not allowed, not analyzed)	Research support from Integrated Therapeutics Group, Inc.	Fair to poor
Simons et al., 2000	Attrition yes (no dropouts), others no.	No dropouts	Yes (No dropouts)	NR	NR	Fair
Weiler et al., 2000	Attrition yes, others no	No.	Yes	No.	Grant from Hoescht Marion Roussel, and from NIH.	Fair

Evidence Table 6. Quality assessment of allergic rhinitis trials in adults with less than 14 days' followup

External Validity

Author Year Country Trial Name (Quality Score)	Number screened/ eligible/ enrolled	Run-in/Washout	Class naïve patients only
Passalacqua et al., 2004	NR/NR/23	At least one week washout between treatments.	NR
Satish et al., 2004	NR/NR/48	No	NR
Simons et al., 2000	NR/NR/15	At least one week washout between treatments.	NR
Weiler et al., 2000	71/NR/41	No	NR

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Head-to-head trials				
Guerra 1994 Italy	RCT, DB, Parallel-group	CIU Above the age of 12 years.	The exclusion criteria ere pregnancy or breast-feeding, steroid dependency, urticaria due to physical agents or angioneurotic oedema, idiosyncratic reaction to antihistamine drugs and multiple drug allergies.	Age: 38.8 years 61% female
Handa 2004 India Fair	Randomized, DB Setting NR	CIU Patients with CIU (urticaria wheals for ≥2d/w for 6 consecutive weeks before study entry) aged 17-65 years. Itching had to be moderate and hives present.	Patients suffering from other forms of urticaria and dermographisms as a primary diagnosis; pregnancy and lactation	Mean age: NR Gender: NR Ethnicity: NR

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Head-to-head trials				
Guerra 1994 Italy	L: loratadine 10 mg C: cetirizine 10 mg P: placebo	NR	Pts recorded in daily diaries. Pts were seen 3, 7, 14, and 28 days after the start of treatment when evaluations were made of clinical symptoms (a 4-point scale being used to evaluate pruritus, erythema, lesion type and size of largest lesion), the interference of the disease in the pts daily activities, therapeutic results and any side effects, and patients compliance with protocol.	1/NR/unclear
Handa 2004 India Fair	C: Cetirizine 10 mg qd F: Fexofenadine 180 mg qd 28-day treatment period	No other topical or systemic medication for CIU was allowed.	Assessments on days 14, 28; analog rating patient's symptoms (0=none, 3=severe, very annoying, disturbing sleep or daily activities)	19/0/97

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Results
Head-to-head trials	
Guerra 1994 Italy	TSS: A vs B: significant p<0.01 days 3,14,28 Day 3/7/14/28 (*estimated from figure): L:: -23%/ -46%/ -65% / -81% C: -35%/ -50%/ -60% / -69% P: -19%/ -23%/ -34% / -55% Active treatment significant vs. P, p<0.05 Responders: L asymptomatic vs. C: 63% vs 45%, NSD; P was significantly worse at 13% (p< 0.05)
Handa 2004 India Fair	Symptom-free at endpoint: C: 27(51.9%) vs F: 2(4.4%) (p NR) Partial improvement at endpoint: C: 19(36.5%) vs F: 19(42.2%) (no p-value) No improvement at endpoint: C: 6(11.5%) vs F: 24(53.3%) (p-value NR) Complaints of increase in intensity of itching, wheals: At night: 35(36.1%) vs Daytime: 51(52.6%)

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Placebo-controlled trials				
Kaplan 2005 USA Fair	RCT, DB, parallel-group Multicenter	CIU Patients aged >12 years, diagnosed with active CIU, with a history of >3 wheals weekly for 6 consecutive weeks and rating of pruritus within last 12 months as at least moderately severe.	Pregnancy and lactation, women without reliable medical or barrier contraception, mental illness, malnutrition, blood dyscrasia, renal of hepatic insufficiency, chronic infection, drug/alcohol abuse, malignancy, malabsorption, history of hypersensitivity/unresponsiveness to study drug or similar drugs, treatment with any investigational product in prior 30 days, serious cardiovascular hepatic, endocrine or other major systematic disease	97% aged <65 years 26% male White: 72% Black: 11% Asian/Oriental: 4% Other: 14%

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Placebo-controlled trials				
Kaplan 2005 USA Fair	F: Fexofenadine 180 mg qd P: Placebo qd 28-day treatment period	NR/ NR	Patient diary was completed bid, recording symptoms and adverse events. Weekly visits to collect data; safety assessments taken at baseline and endpoint. Primary outcome was change from baseline in mean daily number of wheals and the mean daily severity or pruritis score over 28d (rated 0-4, 0=none, 4=very severe). Secondary outcomes were patients assessment of the number, frequency, size, duration of lesions, and the severity of pruritis, each assessed 0-3 scale. Modified TSS was the sum of these 5 scores, calculated bid. Patient and investigator independent global evaluations of overall efficacy of treatment on (scale 0=no improvement or worsening, 4=complete disappearance of symptoms).	Withdrawals: F 7%, P 14%/ NR/ 259

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Results
Placebo-controlled trials	
Kaplan 2005 USA Fair	Mean daily number of wheals: F -0.78, P -0.4, p<.001 Change from baseline in mean pruritis score (0-4): F -1.04, P -0.57, p<.001 Mean reductions in TSS daily scores F>P, p<.001 Global evaluations, both by patient and investigator: F>P, p<0.001

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Monroe 2003 North America, South America, Europe	RCT, DB, parallel-group, multicenter	CIU Patients aged 12 years or older, of either sex and any racial group, with documented signs and symptoms of CIU for 6 weeks or more; CIU flare for 3 weeks or more before screening, with urticarial lesions visible 3 days or more per week. Overall severity had to be at least moderate at screening and baseline, patients had to have at least moderate pruritis, and hives had to be apparent at screening; total reflective pruritus score of 14 or greater over the last 3 days of the screening period and the morning of the baseline visit. Routine laboratory test results and ECG parameters obtained during screening had to be within clinically acceptable limits. Women of childbearing age had to have a negative serum pregnancy test result at screening and use an acceptable method of birth control throughout the trial.	Concomitant illness or required pharmacologic treatment that could interfere with the status of their CIU; previous nonresponse to antihistamines, 2 or more drug allergies, previous intolerance of desloratadine or other antihistamines, need for long-term inhaled or oral corticosteroids in patients with asthma, investigational drug therapy within 30 days, chronic urticaria due to physical factors or food allergy, and pregnancy or breast feeding. Patients who were unable to keep an accurate diary of disease symptoms were also excluded from the study.	40.5 years (range 13-84) 24.7% male 70.8% white, 4.0% black, 6.6% Asian, 16.4% Hispanic, 2.2% other

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Monroe 2003 North America, South America, Europe	D: desloratadine 5 mg P: placebo	NR	Efficacy and safety assessments at day 4 and weeks 1, 2, 4, 6. Patients provided with diary cards at screening, baseline, and weeks 1, 2, and 6. Diary cards were completed twice daily and were collected and reviewed at baseline and visits 3-7. CIU signs and symptoms (pruritus, number of hives, size of largest hive in cm, interference with sleep, and interference with daily activities) evaluated using 4-point scales. Severity of CIU assessed jointly by the investigator and patient/guardian at all study visits (4-point scale; 0=none, 1=mild, 2=moderate, 3=severe). Therapeutic response to study medication also assessed jointly by investigator and subject/guardian at visits 3-7 (1=complete relief, 2=marked relief, 3=moderate relief, 4=slight relief, and 5=treatment failure).	51/3/226

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Results
Monroe 2003 North America, South America, Europe	Mean improvement from baseline in patient-evaluated mean AM/PM reflective pruritus score over first 7 days of treatment: D: 1.05 (47.9%) P: 0.52 (21.9%) p<0.001 Improvement in instantaneous TSS over first 7 days: D: 42.8% P: 24.3% p=0.004 Improvement in AM/PM reflective TSS over days 1-8: D: 43.3% P: 21.4% p<0.001 Improvement in interference of CIU with sleep at days 1-8: D: 44.0% P: 14.4% p=0.007 Improvement in interference of CIU with daily activities at days 1-8: D: 46.9% P: 17.2% p=0.001 Improvements on the above outcomes were seen by the first evaluation (day 2; 24 hours after first dose) Joint patient/investigator assessment of overall condition of CIU found D significantly better than P at all time points (p<0.001, data NR)

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Active-controlled trials				
Breneman 1996 USA	RCT, DB, DD, placebo-controlled, parallel-group, multi-center	CIU Pts at lease 12 years of age with a documented history of chronic idiopathic urticaria that had occurred episodically for at least 6 weeks were studied. To qualify, pts were required to be symptomatic immediately before study entry.	Pts who were using concomitant antihistamines within 36 h prior to the start of the study; tranquilizers, hypnotics, antiepileptics, antidepressants, and agents that act on central nervous system within 1 wk of the start of the study; or astemizole within 6 wks of the start of the study were excluded; as were pts with asthma who required therapy using other means than an inhaled bronchodilator.	Age range: 34.5-38.8 69% female

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to fu/analyzed
Active-controlled trials				
Breneman 1996 USA	C: cetirizine 10 mg qd H: hydroxizine 25 mg tid P: placebo	NR	Pts recorded the symptoms of urticaria experienced: total number of lesions 0 (none) to 3 (greater than 20); number of separate episodes more than one hour apart 0 (none) to 3 (greater than 3); average size of lesions 0 (none) to 3 (greater than 2.5 cm); average duration of lesions 0 (none) to 3 (greater than 12 h); and pruritus 0 (none) to 3 (severe, constant) in daily diary cards. Investigators and pts assessed efficacy by evaluation of symptoms and by global evaluations.	7/NR/188

Evidence Table 7. Urticaria trials in adults

Author Year Country Quality Score	Results
Active-controlled trials	
Breneman 1996 USA	TSS: C + H significant vs. P, p<0.006. *estimated from figure C vs H vs P: -8.5 (-64%) vs -8.7 (-68%) vs -5.3 (-42%) All other significant weeks 1-4 active treatment vs. P for lesion episodes (p=0.001), number/size/ itching (p<0.05), or duration (p=0.001). Onset: C significantly better at day 1 than H in mean number of episodes greater than 1 hour apart (p<0.002). Responders: Definite or complete improvement significant active treatment vs. P (p<0.001).

Evidence Table 8. Quality assessment of urticaria trials in adults

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Head-to-head trials							
Guerra 1994	Yes, method not reported	NR	Yes	Yes	NR	NR	Yes
Handa 2004	Method not reported	Method not reported	NR	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Placebo-controlled trials							
Kaplan 2005	Method not reported	Method not reported	Yes (for 255/259 in ITT population)	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes ('patients received double-blind study medication packages"
Active-controlled trials							
Breneman 1996	Method not reported	NR	Yes	Yes	Yes	NR	Yes
Di Lorenzo 2004	Method not reported	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes

Evidence Table 8. Quality assessment of urticaria trials in adults

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding
Head-to-head trials					
Guerra 1994	NR	Yes	Yes	NR	NR
Handa 2004	Attrition reported, but reasons NR; cross-overs, adherence, and contamination NR	No; 19/116 left the study (16%)	No, analyzed completers only 97/116 (84%)	NR	NR
Placebo-controlled trials					
Kaplan 2005	None were explicitly reported. It appears that 4 patients dropped out of study.	No (attrition 29/259)	No- excluded 4 patients from ITT analysis; imputed through LOCF for other dropouts.	NR	Study sponsored by Sanofi-Aventis Pharma, Bridgewater, NJ. Four of the authors were affiliated with Sanofi-Aventis Pharma
Active-controlled trials					
Breneman 1996	NR	No, 5%	Yes	NR, NR	NR
Di Lorenzo 2004	Attrition reported, but reasons NR; cross-overs, adherence, and contamination NR	Yes; 62/160 discontinued study, all from groups B and D	No; attrition 39%, unclear if cross-overs	NR	Grants from the Ministero Italiano Universitya e Ricerca; no support from the pharmaceutical industry

Evidence Table 8. Quality assessment of urticaria trials in adults

		External Validity				
Author Year	**Quality Rating**	**Number screened/eligible/enrolled**	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Relevance**
Head-to-head trials						
Guerra 1994	Fair	Yes	Yes	No	Yes	
Handa 2004	Fair	NR/NR/116	NR; NR	NR	NR	Unclear
Placebo-controlled trials						
Kaplan 2005	Fair	483/358/259	2-5-day single-bind, placebo run-in; unclear what criteria were used to evaluate the run-in period. However, 358 patients entered run-in and only 255 patients were randomized (no explanation given).	NR	NR	Unclear
Active-controlled trials						
Breneman 1996	Fair	NR	NR; NR	No	Yes	
Di Lorenzo 2004	Poor; very high attrition for unclear reasons; patients 'selected' into study	NR/NR/160. participants 'selected' from university outpatient clinic for study	No; NR	NR	NR	Unclear

Evidence Table 8. Quality assessment of urticaria trials in adults

Internal Validity

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Juhlin 1988	Not described as randomized; no details on how groups selected, although is cross-over study	NA	NR	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Kontou-Fili 1990	Method not reported	Method not reported	NR	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Monroe 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sharpe 1993	Method not reported	Method not reported	NR	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Zuberbier 1995 Cholinergic urticaria	Method not reported	Method not reported	NR	Yes	NR; study reported as 'double blind" during treatment period (A or B) and single-blind when C delivered	NR; study reported as 'double blind" during treatment period (A or B) and single-blind when C delivered	NR; study reported as 'double blind" during treatment period (A or B) and single-blind when C delivered
Zuberbier 1996, cholinergic urticaria	Unclear "randomization list"	Method not reported	NR	Yes	NR; study reported as 'double blind"	NR; study reported as "double blind"	NR; study reported as "double blind"

Evidence Table 8. Quality assessment of urticaria trials in adults

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding
Juhlin 1988	Attrition 19/30; crossovers, adherence, and contamination NR	High-17/30	No, high attrition	NR	NR; second author from UCB Braine-l'Alleud, Belgium
Kontou-Fili 1990	Attrition 1/11; others NR	No, 1/11	No, attrition=1, crossovers NR	NR	NR
Monroe 2003	Attrition and adherence yes; others NR	No (3/226)	Yes	NR	Schering-Plough Research Group
Sharpe 1993	Attrition 2/21; others NR	No, 2/21	No, attrition=2	NR	NR
Zuberbier 1995 Cholinergic urticaria	Yes (1/25); others NR	No, 1/25	No, attrition=1 ; crossovers NR	Yes, 1/25 as did not fit inclusion criteria	NR; one author from UCB Braine-l'Alleud, Belgium
Zuberbier 1996, cholinergic urticaria	None were explicitly reported; 2 patients were excluded for lack of compliance with B (placebo)	Yes (2/11)	No; attrition=2	Yes: 2 patients were excluded for lack of compliance, both in B	NR; one author from UCB Braine-l'Alleud, Belgium

Evidence Table 8. Quality assessment of urticaria trials in adults

		External Validity				
Author Year	**Quality Rating**	**Number screened/eligible/enrolled**	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Relevance**
Juhlin 1988	Poor; unclear if randomized, no information on how groups assigned; no wash-out between cross-over; attrition 19/30	NR/NR/30	none; no washout between treatment in cross-over study	No, all were treated with various antihistamines in past	NR	Unclear
Kontou-Fili 1990	Poor: baseline comparability NR; attrition 1/11	NR/NR/11	None; washout 14d between treatments (at crossover)	NR	NR	Unclear
Monroe 2003	Good	NR/NR/226	None	NR	NR	Unclear
Sharpe 1993	Poor: baseline comparability NR; attrition2/21	NR/NR/21	3-day wash-out period before commencing study and at cross-over	NR	NR	Unclear
Zuberbier 1995 Cholinergic urticaria	Poor; treatment with placebo was single-blind, no baseline characteristics reported, randomization and allocation concealment methods NR	NR/NR/25	None; washout (placebo) 21d between active treatments (at crossover)	No; 16/24 treated with antihistamines in the past	NR	Unclear
Zuberbier 1996, cholinergic urticaria	Poor: high attrition (15%), no ITT, baseline characteristics not reported by group (unable to determine if groups by order of administration were similar);	NR/NR/13	None; 1 week wash-out as only last 2 of 3 weeks of treatment were considered	NR	NR	Unclear

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Active-controlled trials			
Cetirizine			
Tinkleman 1996 USA (Fair)	RCT, not blinded, parallel multicenter	SAR Children with a documented history of SAR during the grass pollen season and currently symptomatic; if they had concomitant mild-to-moderate asthma, they had to have a baseline forced expiratory flow of ≥75% of predicted value. Allergy to grass pollen had been verified by skin test (prick, intradermal, or radioallergosorbent) within 2 yrs before the start of the study. Entering pts were required to have a total score of ≥6 (on a range of 0-18) from the investigating MDs baseline assessment of 6 rhinitis symptoms, with a score of ≥2 for sneezing or nasal discharge and ≥1 other symptom.	Concomitant disease that could interfere with evaluation (e.g., acute sinusitis, nasal polyps), history of severe asthma during pollen season, significantly abnormal blood, renal, or hepatic function, hypersensitivity to study drugs or hydroxyzine, use of antihistamines, on immunotherapy, chronic medication use other than for asthma, asthma therapy in prior 2 months with beta-agonists or steroids
Loratadine			
Boner 1989 Italy (Fair)	NR Single center	SAR Children with moderate and severe SAR, symptomatic at baseline, with their hypersensitivity confirmed by allergy history and a (+) response to skin prick test (allergen wheal diameter 3mm> histamine control) to seasonal allergen (grass pollen, parietaria. Children or parents had to be capable of recording the daily symptom score on a diary card, complying with the dose regimen, and able to maintain the study evaluation schedule.	Asthma; on immunotherapy; nasal polyps; abnormal laboratory test parameters; multiple drug allergies; history of reaction to antihistamines; antihistamine or decongestant use in last 24h prior to randomization; cromolyn sodium, terfenadine, or astemizole within last 2 weeks; or corticosteroids within last month

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Active-controlled trials			
Cetirizine			
Tinkleman 1996 USA (Fair)	Allowed only these medications for chronic asthma: theophylline, inhaled cromolyn or inhaled bronchodilators; excluded beta-agonists or steroid therapy within 2 months prior to study	Mean age: 8.8y Range: 6-11 y 68.3% Male White: 82.3% Other races: 17.7% Mean weight: 74.5 lb; (% ≥ 25 kg: 86.5%) % who were asthmatic: 62.9% Mean duration of allergy: 5.6y Baseline TSS score: 5.8	C1: Cetirizine 5mg for patients <25kg and 10mg for patients ≥ 25kg qd (n=63) C2: Cetirizine 2.25mg for patients <25kg and 5mg for patients ≥ 25kg bid (n=63) Ch: Chlorpheniramine 2 mg tid (n=62)
Loratadine			
Boner 1989 Italy (Fair)	NR	Mean age: 7.7y Range: 4-12 y 65% Male Ethnicity: NR Mean weight: 28.6 kg Mean height: 123.7 cm	L: Loratidine 5 mL (5 mg) (1 mg/mL suspension) qam at same time for 14 days (range: 2.5-5 mg/d) (n=21) D: Dexchlorpheniramine 2.5 mL (1 mg) (1 mg/2.5 mL syrup) q8 h for 14 days (range: 1.5-3 mg/d) (n=19) Children <6y or weighing <20 kg received half dose

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Active-controlled trials			
Cetirizine			
Tinkleman 1996 USA (Fair)	Diary cards were to be filled out each morning and evening Symptoms (sneezing, nasal discharge, itchy eyes, itchy nose/mouth/throat, conjunctivitis, and nasal congestion) were assessed by both patients and investigators as 0:"none", 1:"mild", 2:"moderate", 3:"severe". Those with concomitant asthma rated severity of asthma as: 1: "much worse', 2:"slightly worse", 3:"same", 4:"slightly better", 5:"much better than usual" TSS score; total symptoms severity score calculated from patient diary records; assessed at baseline, day 7, and day14 Global investigator efficacy (scale 0-3): 0 - completely ineffective, 1 - slightly effective, 2 - quite effective, 3 - extremely effective	NR/ NR/ 188	4/ 1/ 186
Loratadine			
Boner 1989 Italy (Fair)	Clinical symptoms evaluated at baseline and day 3, 7, and 14; the severity of each symptom and the overall condition of rhinitis were rated and scored from 0 = none to 3 = severe. Overall therapeutic response was scored from 0:"treatment failure" to 4:"excellent, virtually all symptoms eliminated"	NR/ NR/ 40	4/ NR/unclear

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Results
Active-controlled trials	
Cetirizine	
Tinkleman 1996 USA (Fair)	Primary outcome: Mean change in patient-reported TSS score (except for nasal congestion): C1: -2.6 C2: -2.6 Ch: -2.6, NSD among groups Mean change in individual symptom score between day 0 and day 14 C1 vs C2 vs Ch (NSD for all 6 symptoms): (*all values estimated from graphs)* Sneezing: -0.5 vs -0.67 vs -0.5 Runny nose/post-nasal drip: -0.66 vs -1.0 vs -0.8 Itchy eyes: -0.6 vs -0.7 vs -0.4 Itchy nose, mouth or throat: -0.75 vs-0.75 vs -0.67 Teary or swollen eyes: -0.22 vs-0.21 vs -0.22 Stuffy nose: -0.75 vs -0.93 vs -0 Mean reduction in investigators' mean TSS scores, C1 vs C2 vs Ch: -3.5 vs -3.6 vs -3.8, NSD for all comparisons
Loratadine	
Boner 1989 Italy (Fair)	Mean TSS, day 0 to 14, L vs D: -6.9 points vs -8.2 points, NSD (estimated from graph) Mean individual SS, day 0 to 14, L vs. D: -2.5 points vs -1.8 points, NSD (estimated from graph) TSS, as assessed by both investigator and patient/parent, decreased in both L and D, with NSD between groups (p=0.295 in favor of D)

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Jordana 1996 Canada (Fair)	RCT, DB, parallel multicenter	SAR Patients 12-17y with a history of moderate to severe ragweed-induced SAR who had allergy confirmed with a ragweed skin-prick test (wheal and flare response with a wheal ≥ 3mm in diameter greater than buffer control).	Concurrent PAR; if they had taken long-acting H1 antagonists within the past 6w, inhaled intranasal or systemic corticosteroids, inhaled sodium cromoglycate within last 4w, loratadine or other OTC antihistamine within last week; received any other therapy for rhinitis (time frame unclear); clinical evidence of infection of sinuses or upper or lower respiratory tract.; nasal surgery in last year, structural abnormalities or nose; pregnant; lactating, not using reliable contraceptive measures
Placebo-controlled trials			
Cetirizine			
Allegra et al. 1993 Europe (Fair)	PCT, DB, parallel multicenter	SAR Children between 2-6y with pollen-induced SAR, which was based on child's history, one positive allergy test (prick test, RAST, or CLA) and the presence of at least 3 of the following 5 symptoms: sneezing, rhinorrhea, blocked nose, nasal pruritus, ocular pruritus, rated 0-3. A TSS of ≥6 was required for inclusion.	Vasomotor or infectious rhinitis, obstructive nasal polyposis, infection requiring antibiotic therapy, history of relevant drug allergy, clinically relevant systemic illness or unexplained laboratory test abnormalities. Patient could not use other antihistamines, sedatives, nasal decongestants, topical preparations for nose or eye, or corticosteroids (other than by oral inhalation for asthma)

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Jordana 1996 Canada (Fair)	Terfenadine 60 mg, naphazoline and pheniramine combination eye drops, and bronchodilator salbutamol were the only rescue drugs allowed	Mean age: NR Range: 12-17y 56.25% male Ethnicity: NR Asthma: A 46/119, B 45/121	L: Loratadine 10 mg syrup qam + placebo spray F: Fluticasone propionate 200 micrograms aqueous spray qam + placebo tablet 4-week treatment period
Placebo-controlled trials			
Cetirizine			
Allegra et al. 1993 Europe (Fair)	Children with asthma could continue theophylline, beta2 sympathomimetics, inhaled cromoglycate, nedocromil, or inhaled corticosteroids (≤ 200 micrograms/day)	Mean age: 4.45y Range: 2-6y 69% male Ethnicity: NR	C: Cetirizine 5 mg qd (10 drops of a 10 mg/mL solution) P: Placebo solution of same color and taste 2-week treatment period

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Jordana 1996 Canada (Fair)	Patients visits at day 0, after 2 and 4 weeks of treatment, and 2 weeks after study completion Symptom-free days for nasal blockage was primary outcome (score of 0); patients given daily symptom diary cards, scale 0 (absent) to 3 (severe): nasal blockage on awakening, nasal blockage for rest of day, sneezing, nasal itch, eye watering or irritations recorded int he evening	NR/ 257/ 242	12/unclear/240 ; 2 withdrawn prior to randomization; 12 pts were discontinued from the study for AEs, and 5 for ineffective treatment
Placebo-controlled trials			
Cetirizine			
Allegra et al. 1993 Europe (Fair)	Parent completed daily diary cards assessing severity of symptoms (0=none, 3=severe) Investigators rated symptoms on same scale on each visit and at final visit. At final visit investigator made global assessment of efficacy using 5-point scale (0=worse, 5=excellent response, complete disappearance of symptoms) Disease Severity Score (DSS): maximum score of any one of the 5 symptoms evaluated (i.e., the score of the most troublesome symptom) computed each day per parent's evaluations and at each visit per investigator evaluations. Cumulative frequency of the DSS from parents' daily record was calculated fro each patients over the 2-week treatment period and expressed as a % of days with a maximum score of 0 (no symptoms), 1 (mild symptoms) and 2 (moderate).	NR/ NR/ 107	0/ 0/ 107

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Results
Jordana 1996 Canada (Fair)	Symptom-free days (%): F> L for all nasal symptoms; NSD for eye-watering or eye-irritation SS F< L for all nasal symptoms; NSD for eye symptoms. Rescue-free days (%), L vs F: 96 days vs 93 days, NSD Patients receiving rescue antihistamines (% of patients), L vs F: 39% vs 21%, p<0.0025 NSD between groups for use of rescue eye drops or rescue bronchodilator Nasal peak inspiratory flow: F>L both in am (p=0.0051) and pm (p=0.0036) (n=56, chosen randomly from study population)
Placebo-controlled trials	
Cetirizine	
Allegra et al. 1993 Europe (Fair)	Results given as C vs P: Change in mean DSS (assessed by investigator) between baseline and last visit: -1.4 vs -1.1, p = 0.040 Group C associated with parent-assessed scores ≤ 1(ie, mild or absent symptoms) more often than P, p=0.002 Global evaluation of rhinitis by investigators: excellent or good: 63% vs 45.3%, p = 0.039

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Ciprandi et al, 1997a **Ciprandi** 1997b (cough) Italy (Fair)	Randomized, double-blind, parallel group, single center	SAR Children ages 6 to 15 years with allergic rhino conjunctivitis; a history of allergic rhino conjunctivitis due to Parietaria Judaica and/or grass pollen for at least 2 previous seasons, without clinical asthma. Skin-prick test and RAST confirmed the diagnosis.	History of asthma or previous documented intolerance to the studied drug; any other ocular or nasal disease
Masi 1993 Italy (Fair)	Randomized, DB, parallel group, multicenter	SAR Children 6-12 y with pollen-associated allergic rhino-conjunctivitis, diagnosed on the basis of a reliable history, a positive allergy test for prevailing pollen (skin test or RAST) within the previous year and the presence of ≥3 of these symptoms: rhinorrhea, sneezing, blocked nose or pruritus involving nose or eyes (scaled 0-3). TSS had to be ≥8 as assessed by investigator at first visit.	Infectious or vasomotor rhinitis, recent URTI, sinusitis, otitis media, obstructive nasal polyposis, any infection requiring antibiotic therapy, history of sensitivity to study drugs, any illness that might interfere with the assessment of therapeutic response or laboratory tests

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Ciprandi et al, 1997a **Ciprandi** 1997b (cough) Italy (Fair)	Subjects did not receive topical and/or systemic drugs during the preceding 6 weeks, they had not received specific immunotherapy before and during the study.	Mean age: 8.5y Range 6-15 55% male Ethnicity: NR	C: Cetirizine 0.15 mg/kg qam P: Placebo qam
Masi 1993 Italy (Fair)	Children with asthma could continue theophylline, beta2 sympathomimetic drugs, inhaled cromoglycate, nedocromil or inhaled corticosteroids (<200 mcg/d) provided dose unchanged throughout study. Sedative and topical preparation for nasal or ocular use were prohibited.	Mean age: 10.15y 61.3% male Ethnicity : NR	C: Cetirizine 5 mg bid P: Placebo 2 week treatment period

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Ciprandi et al, 1997a **Ciprandi** 1997b (cough) Italy (Fair)	Rhinitis symptoms and possible adverse events were recorded in the evening on a diary card; signs and symptoms (ocular hyperaemia, itching, lacrimation, eyelid swelling, nasal itching, obstruction, rhinorrhea, sneezing) graded on a 4-point scale; cough was also reported on a 4 point scale. Patients underwent 2 clinical visits, at the beginning and end of the study (4 weeks). A nasal lavage was performed at each visit.	NR/NR/20	0/0/20
Masi 1993 Italy (Fair)	Patients kept daily symptom diary Disease Severity Score: the maximum score (i.e. most troubling symptom) of any of the 5 symptoms (rhinorrhea, sneezing, blocked nose, pruritis involving nose or eyes), each assessed on a 0-3 scale (0= no symptoms, 3=severe) Cumulative frequency of the DSS: calculated as a % of study days when DSS was 0 (no symptoms, ≤1 (symptoms mild to moderate, and ≤2 (symptoms absent to moderate). % days when DSS ≤1: primary outcome	NR/NR/124	10/ 2/ unclear

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Results
Ciprandi et al, 1997a **Ciprandi** 1997b (cough) Italy (Fair)	Clinical signs and symptoms score: Improved in C vs P at week 1 (p=0.03), 2 (p=0.01), 3 (p=0.01), and 4 (p=0.01) Cough intensity: Improved in C vs baseline at week 2,3, and 4 (p<0.01). C < P at weeks 2 (p<0.02), 3 (p=0.01), and 4 (p=0.02) Cough frequency: C < P at weeks 1 (p=0.03), 2 (p=0.006), 3 (p=0.01) and 4 (p=0.02) PEF, FEV1: NSD Neutrophil (p=0.02) and eosinophil (p=0.01) counts, and intracellular adhesion molecule (ICAM-1) expression in nasal epithelial cells decreased in C compared to baseline; NSD in P
Masi 1993 Italy (Fair)	All data given as C vs P Patient-assessed DSS: % patients ≤2 A: 90.0 B: 75.8 (p=0.0004) Differences in investigator-assessed DSS between baseline and: Week 1: - 1.22 vs -0.87, p=0.007 Week 2: -1.75 vs -1.22, p<0.001 Investigator global evaluation of rhino conjunctivitis: 79% vs 50% patients considered "excellent" or "good" at end of 2 weeks, p<0.001

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Pearlman et al, 1997, **Winder et al**, 1996 (safety) US (Fair)	Randomized, double-blind, parallel group, multicenter	SAR Children ages 6 to 11 years with documented histories of SAR during the fall pollen season; allergy to pollen confirmed by an intradermal or skin prick test or a RAST within 2 years prior to the start of the study. Entering patients were required to achieve a minimum TSS score of 6 (range, 0 to 18) with the investigator's baseline assessment of 6 rhinitis symptoms. TSS included at least 2 symptoms of moderate severity (score 2 or higher), one of which had to be sneezing or nasal discharge.	Patients were excluded if they had diseases that might interfere with the evaluation of the therapeutic response (e.g., recent URI, acute sinusitis, nasal polyposis); history of severe exacerbations of asthma during the pollen season, significantly abnormal hematologic, renal, or hepatic function; hypersensitivity to cetirizine or hydroxyzine; escalating course of immunotherapy or on maintenance therapy for <6m.
Fexofenadine			
Wahn et al, 2003 15 countries: Argentina, Austria, Chile, Finland, France, Germany, Israel, Italy, Poland, Portugal, South Africa, Spain, Uruguay, US (Fair)	Randomized, double-blind, parallel group, multicenter	SAR Children ages 6 to 11 years with spring or fall SAR and an approximate 1-year history of SAR. A positive skin prick test result (wheal diameter 3 mm or greater compared with diluent within 15 minutes of the skin prick) to at least 1 allergen indigenous to the study site area or, when relevant, to a child's site of residence, which must have been positive in serum allergen-specific IgE testing, was required. In addition, the appropriate sensitizing allergen was required to be present at visit 1 and likely to be present for 3 weeks from visit 1. Children also needed to satisfactorily demonstrate that they could swallow the study medication.	Upper respiratory tract infection within 30 days of the study; purulent conjunctivitis or rhinitis of any type other than SAR; obstructive deviated nasal septum or obstructive nasal polyposis; active perennial allergic rhinitis; cystic fibrosis; immunotherapy to treat SAR; and clinically significant cardiovascular, hepatic, neurologic, psychiatric, endocrine, or other major systemic disease; Excluded drugs: corticosteroids: oral (30d prior), nasal (14d), inhaled (30d); cromolyn sodium inhaled or oral (14d) .

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Pearlman et al, 1997, **Winder et al**, 1996 (safety) US (Fair)	Administration of oral steroids or astemizole within 2 months prior to the study was not permitted. Nasal decongestants were discontinued 24h prior, antihistamines for 48h, and cromolyn sodium or intranasal steroids for 2w prior.	Mean age: NR Range 6-11 67% male Ethnicity: 88% white, 11% other	C1: Cetirizine 5 mg qd C2: Cetirizine 10 mg qd P: Placebo qd
Fexofenadine			
Wahn et al, 2003 15 countries: Argentina, Austria, Chile, Finland, France, Germany, Israel, Italy, Poland, Portugal, South Africa, Spain, Uruguay, US (Fair)	Drugs that were excluded included oral, nasal, and inhaled corticosteroids for 30, 14, and 30 days, respectively, before visit 1, and inhaled or oral cromolyn sodium for 14 days before the visit. Between visits 1 and 2, the following drugs were excluded: the H1-receptor antagonists astemizole, loratadine, fexofenadine, and cetirizine; and leukotriene modifiers, such as montelukast and zafirlukast.	Mean age: 9.0y, range 5-12 % male: NR 80% White 7.0% Black 1% Asian, 11% Multiracial	F: Fexofenadine 30 mg bid P: Placebo bid 2-week treatment period

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed
Pearlman et al, 1997, **Winder et al**, 1996 (safety) US (Fair)	Patient diary and physical examination at weeks 1, 2, 3, and 4; each symptom evaluated on a 4-point scale by investigator each week, and by parent/child each day.	NR/NR/209	For efficacy: 4/0/205 For safety: 4/16/189 for ECG analysis: NR/88/121
Fexofenadine			
Wahn et al, 2003 15 countries: Argentina, Austria, Chile, Finland, France, Germany, Israel, Italy, Poland, Portugal, South Africa, Spain, Uruguay, US (Fair)	Symptoms assessed by the child and caregiver immediately before dosing. Diary cards were collected at visits 2, 3, and 4 (though visit 3 was not mandatory). Primary efficacy variable was mean change from baseline in the average PM-reflective TSS. Secondary efficacy variables were AM-reflective TSS, PM and AM reflective individual SAR symptom scores, and the daily PM-reflective TSS.	1961/NR/935	3/NR/932 7 (withdrew for treatment failure), 32 did not complete entire study but had at least one follow-up measure and were analyzed

Evidence Table 9. Seasonal allergic rhinitis trials in children

Author Year Country (Quality Score)	Results
Pearlman et al, 1997, **Winder et al**, 1996 (safety) US (Fair)	Group C2 vs P: Patient-assessed change in mean TSS from baseline (4-point scale; baseline scores not reported) -3.19 vs -2.09 (p<0.05) Individual symptoms Ocular itching: -0.73 vs -0.10 (p<0.05) Oral/nasal itching: -0.74 vs -0.53 (p<0.05) Group C1 vs P: Patient-assessed change in mean TSS from baseline -2.41 vs -2.09 (NSD) Other outcomes not reported for C1 vs P Group C1 vs C2: C2>C1 for relief of ocular itching at week 3 (p<0.05) and relief of oral/nasal itching at weeks 2 and 3 (p<0.05) Investigator-assessed TSS: NSD among treatment groups (data not reported)
Fexofenadine	
Wahn et al, 2003 15 countries: Argentina, Austria, Chile, Finland, France, Germany, Israel, Italy, Poland, Portugal, South Africa, Spain, Uruguay, US (Fair)	Mean change from baseline on pm-reflective TSS, F vs P (4-point scale): -1.94 vs -1.21 (p ≤0.0001) TSS in am: -1.67 vs -0.93 (p<0.0001) Individual symptom scores in pm (sneezing; rhinorrhea; itchy nose, mouth, throat; itchy watery eyes; nasal congestion) all decreased in F vs P (p<0.05)

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Allegra 1993	Yes, computer-generated list	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes
Bender, 2003 US	Method not reported	Method not reported	NR	Yes	NR; "double blind"	NR; "double blind"	Yes (double-dummy, placebo)
Boner, 1989 Italy	Method not reported	Method not reported	Yes; loratadine patients exposed to higher pollen counts, but difference NS (p=0.09)	Yes	Yes	Yes	Parent not masked; unclear if child aware
Ciprandi 1997a Ciprandi 1997b Italy	Method not reported	Method not reported	Yes (no statistics)	Yes	Yes; described as 'double blind' but unclear who was blinded	Yes; described as 'double blind' but unclear who was blinded	Yes; described as 'double blind' but unclear who was blinded

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Allegra 1993	Attrition reported (none). Crossovers, adherence and contamination NR.	No (no attrition)	Yes, assuming no cross-overs	None	NR: Affiliation of last author is UCB Pharma Secotor R & D, B-1420 Braine-l'Alleud, Belgium	Fair
Bender, 2003 US	NR	NR	NR	NR	GlaxoSmithKline	Poor: can't determine if groups were similar at baseline and number analyzed not specified
Boner, 1989 Italy	Attrition reported (4/40); adherence measured but results NR	10% attrition	No, 36/40 analyzed; no reporting of cross-overs	No	NR	Fair
Ciprandi 1997a Ciprandi 1997b Italy	Attrition yes, others no	No	Yes	No	NR	Fair

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	*External Validity* Number screened/ eligible/ enrolled	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Allegra 1993	NR/NR/107	No; washout of appropriate duration prior to entry were prescribed for relevant medications.	NR	NR	Unclear
Bender, 2003 US	NR/NR/60	No/ No medications for SAR allowed 1-2 weeks prior to study entry	NR	NR	Unclear
Boner, 1989 Italy	NR/NR/40	No/ no use of antihistamines or decongestants within 24h prior to initiation of treatment, cromolyn Na, terfenadine or astemizole within the previous 2 wks, no corticosteroid preparations within the previous month	NR	NR	Unclear
Ciprandi 1997a Ciprandi 1997b Italy	NR/NR/20	None	NR	NR	Unclear

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Jordana 1996	Method not reported	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes
Masi 1993	"Block randomization was done according to the order of inclusion into the study"	NR	Yes	Yes	NR; study reported as 'double blind"	NR: study reported as "double blind"	Yes
Pearlman 1997, Winder 1996 (safety) US	Method not reported	Method not reported	Yes	Yes	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Jordana 1996	Attrition reported (12/240); others NR	No; ITT results presented, 240 of 242 analyzed	No, 2 patients withdrew prior to randomization; remainder of patients analyzed	None from ITT group, whose results were presented	Glaxo Canada Inc.	Fair
Masi 1993	Yes; no, yes, no. Of 10 patients not analyzed at follow-up, 4 were due to AE, 2 due to lack of efficacy, 1 protocol violation, 2 lost to follow-up	No (10/124)	All patients were reported to be included in both efficacy and safety analysis	1 due to protocol violation, 2 due to lack of efficacy	NR: third author affiliation is UCB Pharma Secotr R & D, B-1420 Braine-l'Alleud, Belgium	Fair
Pearlman 1997, Winder 1996 (safety) US	Attrition reported, adherence and contamination no	No	No (205/209 analyzed)	2 patients removed for poor compliance and 1 for protocol violation	U.S. Pharmaceuticals Group, Pfizer, Inc.	Fair

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	*External Validity* Number screened/ eligible/ enrolled	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
Jordana 1996	NR/NR/242	No run-in period; certain medications excluded for various pre-study periods: 6-week washout for long-acting histamine antagonists; 4-week washout for inhaled, intranasal, or systemic corticosteroids or inhaled sodium cromoglycate; 1-week washout for loratadine or other OTC antihistamine	"subjects also excluded if they had received any other therapy for their rhinitis…"	NR	Unclear
Masi 1993	NR/NR/124	No; Washouts: astemizole=6 wks; systemic corticosteroids and ketotifen= 2wks, topical corticosteroids and cromones= 1 wk, other antihistamines and decongestants =2days	NR	NR	Unclear
Pearlman 1997, Winder 1996 (safety) US	NR/NR/209	None/Various medications excluded prior to study (see Allowed Medications)	No	NR	Unclear

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Segal 2003	Method not reported	Method not reported	Baseline characteristics reported only for analyzed group only (164/172 analyzed)	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes
Tinkelman 1996	Method not reported	Yes (drug dispensed by nurse independent of investigator)	Yes	Yes	NR	NR	No
Wahn 2003; Meltzer 2004 15 countries	Method not reported	Not reported	More males in placebo group; otherwise similar.	Yes	Yes; described as 'double blind' but unclear who	Yes	Yes

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Segal 2003	16 patients discontinued treatment during study, usually due to unrelated intercurrent illness.	Attrition 16 (9.3%) and 8 post-randomization exclusions. Only patients <25kg were analyzed (n=146), as too few patients in the <25kg group.	No, attrition and post-randomization exclusions	8 patients excluded from efficacy analysis: 7 due to protocol violations, 1 withdrew before onset of study.	Pfizer Inc., New York, New York	Poor: post-randomization exclusions, exclusion of nasal congestions from TSS, baseline characteristics NR for entire group
Tinkelman 1996	Attrition reported (6/188); adherence NR	No	No, 182/186 analyzed; no mention cross-overs	No	U.S. Pharmaceuticals Group, Pfizer Inc,, New York, NY	Fair
Wahn 2003; Meltzer 2004 15 countries	Attrition and adherence yes, contamination no.	No	No (932/935 analyzed); only analyzed if compliant with medications and data available	Excluded if noncompliant with medications after randomization	Aventis Pharmaceuticals	Fair

Evidence Table 10. Quality assessment for seasonal allergic rhinitis trials in children

	External Validity				
Author Year	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Relevance**
Segal 2003	NR/NR/172	NR/NR	NR	NR	Unclear
Tinkelman 1996	NR/NR/188	NR/ "patients taking medications that could interfere with the study were instructed to discontinue them for appropriate washout periods before entry"	NR	NR	Unclear
Wahn 2003; Meltzer 2004 15 countries	1961/NR/935	5- to 9-day single blind, placebo run-in; required to have an average TSS of 5 or higher for the last 2 7:00 pm reflective TSSs (excluding nasal congestion) to qualify for randomization; required to be compliant with medications (miss 0 or 1 tablets)	NR	NR	Unclear

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Head-to-head trials			
Sienra-Monge 1999 Mexico Fair	RCT, DB Single center	PAR Children age 2 to 6 years with PAR verified by the presence of a (+) radioallergosorbent test to house dust mites or plant pollens. Each patient had to have at least 3 of 5 major rhinitis symptoms (rhinorrhea, sneezing, nasal congestion, nasal pruritus, or ocular pruritis) and a combined symptoms severity score of 8 when each symptoms was rated by the investigator on a scale of 0 (none) to 3 (severe).	Excluded patients who were already receiving antihistamines, steroids, or immunotherapy. Also excluded were pts with major systemic disease, recent respiratory illness, or significant nasal anatomic abnormalities.
Active-controlled trials			
Cetirizine			
Hsieh J-C 2004 Taiwan Fair	RCT, DB, placebo-controlled	PAR Children aged 6 to 12 years with a known history of moderate to severe PAR for ≥1 year. Any specific allergy to house dust mite was confirmed by a positive skin-prick test response to house dust mites and a mite-specific IgE response.	A positive response to any other allergen; nasal abnormality, concurrent purulent nasal infection, any other significant medical condition.

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Head-to-head trials			
Sienra-Monge 1999 Mexico Fair		Mean age 4.4y (SD 1.2) 63% male Ethnicity NR	C: Cetirizine suspension 0.2 mg/kg qd L: Loratadine suspension 0.2 mg/kg qd Treatment duration 28d
Active-controlled trials			
Cetirizine			
Hsieh J-C 2004 Taiwan Fair	Any current medication affecting any allergy symptom was discontinued as appropriate	Mean age: (A) 8.05y, (B) 8.2y, (C) 8.05y % Female: (A) 40%, (B) 35%, (C) 45% Ethnicity NR	C: Cetirizine 20 mg qd M: Montelukast 5 mg qd P: Placebo qd Treatment duration 12 weeks

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Head-to-head trials			
Sienra-Monge 1999 Mexico Fair	Primary outcome was histamine skin test. Secondary outcomes: VAS; eosinophils in the nasal smear; investigator; parent and patient symptom assessments Symptom evaluations at baseline and after 28 days by the investigator; parents completed symptom assessments at baseline and on each day of the study in symptom diaries. The investigator provided a global assessment of therapy using a VAS with a 100-point scale.	NR/NR/80	NR/NR/78
Active-controlled trials			
Cetirizine			
Hsieh J-C 2004 Taiwan Fair	Patients recorded all symptoms in a diary card qd for 7d prior to study entry and a rhinitis symptom score was calculated. Pediatric rhino conjunctivitis Quality of Life Questionnaires, serum eosinophil cationic protein level, and nasal expiratory peak flow were measured at baseline and follow-up. Rhinitis symptom score included: 4 nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, sneezing) and 4 non nasal symptoms (eye itching, eye tearing, eye redness, itching of ears or palate). Symptom score rated 0-3 (3, most severe). TSS was sum of both nasal and non nasal symptom scores. Average baseline TSS was mean of 7 daily scores at baseline. At follow-up, mean TSS and individual symptoms scores were based on prior 28 days at weeks 4, 8, and 12.	NR/NR/65	4/1/60

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Results
Head-to-head trials	
Sienra-Monge 1999 Mexico Fair	Global Evaluation Score assessed by investigator (C vs L): -62.8% vs -64.6% (NSD) Histamine prick test (inhibition of wheal response): C>L (p<0.001) Eosinophil count: decreased in both groups, NSD between groups Investigator assessment of individual symptoms (sneezing, rhinorrhea, nasal obstruction, nasal pruritus, ocular pruritus): NSD between groups (both improved) Parent assessment of patient symptoms: both improved, C more effective in relieving rhinorrhea, sneezing, nasal obstruction, and nasal pruritis (p<0.001)
Active-controlled trials	
Cetirizine	
Hsieh J-C 2004 Taiwan Fair	TSS: C<M<P weeks 4,8,12 (p<0.05); Mean rhinorrhea score C and M<P weeks 4,8,12 (p<0.01), C<M weeks 8 and 12 (p<0.01); Nasal itching and sneezing C<P weeks 4,8,12, (p<0.05); Mean red-eyes scores C<P weeks 8 and 12 (p<0.01); NSD among groups itching throat and watery eyes NPEF: M>C>P weeks 4,8,12. C>P weeks 8 and 12 (p<0.05) QOL: Improved in C and M >P at 12 weeks (p<0.01) Eosinophil % of nasal smear: C and M<P at 12 weeks (p<0.01)

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Lai 2002 Taiwan Fair	RCT, DB, parallel	PAR Children 6 to 12y with ≥1y history of moderate to severe PAR, with a (+) prick test response to house-dust mite and a (+) response to mite-specific IgE; no other significant medical condition or nasal abnormality	Significant other medical condition which may have affected allergy symptoms
Placebo-controlled trials			
Cetirizine			
Baelde 1992 Belgium (Fair)	Randomized, DB, parallel group, multicenter	PAR Children ages 2 to 14 years who had suffered from well-documented PAR for ≥2y; (+) skin tests and/or radioallergosorbent tests for allergens other than pollen and at least 2/ 5 principal symptoms of PAR (nasal obstruction, rhinorrhoea, nasal pruritis, sneezing, and pharyngeal drip)	

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Lai 2002 Taiwan Fair	No	Mean age: 8.07 y Range: 6-12 y 43.5% male Ethnicity; NR Mean weight: 29.4 kg	C: Cetirizine 10 mg qd (n=20) K: Ketotifen 1 mg/bid (n=20) O: Oxatomide 1 mg/kg bid (n=20) P: Placebo (n=20) Treatment duration 12 weeks
Placebo-controlled trials			
Cetirizine			
Baelde 1992 Belgium (Fair)	Children with co-existing allergic disorders were eligible for inclusion if they were not on any treatment other than the study drug. Patients with asthma were permitted to take sodium cromoglycate, inhaled beta-2 sympathomimetics or inhaled corticosteroids to a maximum dose of 400 mcg per day. Patients could not take other antihistamines, corticosteroids, anticholinergics, sedatives, adrenergic agens, antiinflammatory agents or aspirin during the study period.	Mean age 8.6 y (sd 2.2) 67% male Ethnicity: NR	C1: Cetirizine 5.0 mg bid C2: Cetirizine 2.5 mg bid P: Placebo bid

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Lai 2002 Taiwan Fair	Nasal symptom scores in a diary card (which incorporated presence of a nocturnal cough) and a Pediatric Rhino conjunctivitis Quality of Life Questionnaire (PRQLQ) Total nasal symptom score (TSS): rhinorrhea, nasal stuffiness/congestion, nasal itching, sneezing, eye itching/burning, eye tearing/watering, eye redness, itching of ear or palate Patients reported scores for weeks 4, 8, and 12	NR/ NR/ 80	11/ NR/ 69
Placebo-controlled trials			
Cetirizine			
Baelde 1992 Belgium (Fair)	Investigators evaluated every symptom at each clinical visit and rated them on a scale of 0 (absent) to 4 (severe enough to require treatment with drugs other than or in addition to an antihistamine). In addition, investigators made a global assessment of efficacy at the end of treatment using a scale of 0 (aggravation) to 4 (disappearance of all symptoms). Parents completed daily record cards in which they entered the severity of symptoms assessed on a scale of 0 (none) to 3 (severe), side effects, and any additional treatment. Clinical visits at baseline, 1 and 2 weeks.	NR/NR/138	13/NR/125

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Results
Lai 2002 Taiwan Fair	Mean TSS and individual symptom scores of diary card: Multiple posterior analyses of between-group comparisons reported: C, K, and O improved mean TSS from baseline compared to P at 4,8, and 12 w (p<0.01). Lower TSS for C than K and O for week 12 (p<0.05); C, K and O all demonstrated improved individual symptom scores compared to P and results were generally significant (p<0.05). Group C lower scores for mean rhinorrhea and nasal congestion than K, O and P and p-value generally <0.05 for these between-group comparisons Peak expiratory flow rate: higher for group C than for other treatment groups at 12 weeks (p<>0.05) Quality of life: higher for C and K at 12 weeks (p<0.05 vs P)
Placebo-controlled trials	
Cetirizine	
Baelde 1992 Belgium (Fair)	Mean percent change from baseline, assessed by investigator (C1 vs C2 vs P) Nasal obstruction: -47.9% vs -33.2% vs 28.7% (C1 vs P, p=0.03) Rhinorrhea: 59.4% vs 47.3% vs 37.9% (C1 vs P, p=0.03) Sneezy: 68.2% vs 47.3% vs 37.9% (C2 vs P, p=0.04) Pharyngeal drip: 77.2% vs 53.2% vs 54.9% (C1 vs C2, p=0.03) Nasal pruritis: NSD, data not reported Overall average score for all symptoms: C1 vs P p=0.01 Global evaluation by investigators: C1>C2 (p=0.04) and C1>P (p=0.006) Evaluation by parents: NSD C1 vs P or C2 vs PC

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Ciprandi 2001 Italy (Fair)	Randomized, DB, parallel group, single center	PAR Children ages 3 to 10 years who showed isolated sensitization to house dust mite (evaluated by skin testing and RAST), and suffered from perennial rhino conjunctivitis and/or mild intermittent asthma.	Anatomical alterations of the upper airways, immunologic deficiencies, or major systemic diseases (diabetes, anemia, cystic fibrosis, inherited metabolic disorders); history of cardiac disease and/or arrhythmia.

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Ciprandi 2001 Italy (Fair)	Specialists could prescribe some drugs as needed. Patients were allowed to use rescue or symptomatic drugs when needed. Investigators suggested cetirizine (5 mg qd), inhaled albuterol, inhaled fluticasone in case of asthma exacerbations, or short courses of systemic corticosteroids. Any other drug considered appropriate was also allowed.	Mean age: 6.5y Range: 3-10y 75% male Ethnicity: NR	C: Cetirizine 5 mg qhs for 24w P: Placebo qhs for 24w

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Ciprandi 2001 Italy (Fair)	Parents recorded symptoms on diary cards: sneezing, nasal itching, and obstruction, rhinorrhea, lacrimation, conjunctival itching and hyperemia, cough, wheezing, and chest tightness. Symptoms graded with 4-point scale: 0=absent, 1=mild, 2=moderate, and 3=severe. Participants also recorded the number of nights their sleep was disturbed and all treatments taken.	NR/NR/20	0/0/20

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Results
Ciprandi 2001 Italy (Fair)	(Data presented graphically only) Weekly mean rhinitis scores: C<P for 24/24 weeks; for 11/24 weeks, between-group difference significant (p<0.05) Weekly mean asthma symptom scores: C<P for 6/24 weeks (p<0.05); for 10/24 weeks P<C (NSD); for 8/24 weeks C=P Drug intake: C<P for 24/24 weeks (p<0.05 for 16/24 weeks); C consumed less cetirizine (p<0.001), inhaled fluticasone (p<0.01), systemic steroid (p<0.05), and antibiotics (p<0.05) than B

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Placebo-controlled trials			
Cetirizine			
Jobst 1994 Germany, The Netherlands (Fair)	Randomized, DB, parallel group, multicenter	PAR Children ages 6 to 12 years with a documented history of PAR for ≥ 1y with a (+) skin test or RAST for nonseasonal respiratory allergens (e.g., house-dust mite, molds, and cat and dog dander) within the year preceding entry to the study, and symptoms of PAR within the preceding 24 hours.	Presence of pollen- or its predicted appearance with 4 week- to which the patient was allergic; presence of any conditions requiring systemic corticosteroids, such as bronchial asthma (unchanged treatment with the equivalent of 200 mcg betamethasone daily by inhaleation was allowed) and atopic dermatitis; vasomotor or infectious rhinitis; URI within the previous 3 weeks; obstructive nasal polyps or signnificant septal deviation; hypersensitivity to piperazines (e.g., cetirizine, hydroxyzine); clinically relevant renal, hepatic, cardiovascular, or related problems; clinically relevant biochemical abnormalities not linked to PAR; insufficient washout periods; administraion of an escalating course of desensitization therapy; participation in another drug trial within the previous 3 months; recent or foreseeable changes in lifestyle (e.g., changing one's residence, holidays, etc); and assessed risk of noncompliance.
Loratadine			
Yang 2001 Taiwan (Fair)	Randomized, DB, parallel group, single center	PAR Children ages 3 to 12y, with a history of allergic rhinitis due to house dust mites. All children had at least 3 of the following 5 symptoms at enrollment: sneezing, rhinorrhea, nasal congestion, nasal itching and ocular symptoms. Symptoms were graded on a 4-point scale (0=absent, 3=severe). Patients had to be symptomatic with a total symptom score ≥ 7. Sensitivity to dust mites was confirmed by a positive skin prick test and/or a positive CAP result to Dermatophagoides pteronyssinus or Dermatophagoides farinae.	Diseases that might interfere with the study outcome or require specific treatment (such as severe asthma, severe atopic dermatitis, heart failure, renal or hepatic dysfunction); known idiosyncratic reaction to antihistamines, history of multiple drug allergies; patients who received drugs before the enrollment, including ketotifen within 2 weeks, second generation antihistamines within 4 weeks, short acting antihistamines within 4 days, systemic corticosteroids within 2 months, intranasal or eye drops containing a corticosteroid within 2 weeks, anticholinergics within 2 days, topical cromoglycate within one week, and nasal decongestants within 2 days.

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Allowed other medications/ interventions	Age Gender Ethnicity	Interventions
Placebo-controlled trials			
Cetirizine			
Jobst 1994 Germany, The Netherlands (Fair)	Yes; concomitant medications were taken by 26-31% of patients (mainly antiasthmatics, B-agonists, Theophyllin, inhaled corticosteroids) and nasal preparations (sodium cromoglycate [not allowed by protocol but used by 8-9 patients during study])	Mean age group (A) 8.6y, (B) 9.2, (C) 9.3, (D) 8.9 % Male: (A) 54.8, (B) 70.6, (C) 57.9, (D) 57 Race/ethnicity: (D) Caucasian 97.6%	C1: Cetirizine 2.5 mg qd for 2w C2: Cetirizine 5 mg qd for 2w C3: Cetirizine 10 mg qd for 2w P: Placebo qd
Loratadine			
Yang 2001 Taiwan (Fair)	No	Mean age group (A) 6.0y, (B) 6.6y % Male: 57 Ethnicity: NR	L: Loratadine syrup 1 mg/mL; doses adjusted according to body weight (5 mg if body weight < 30 kg, 10 mg if weight >30 kg) P: Placebo, not described

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Method of Outcome Assessment and Timing of Assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Placebo-controlled trials			
Cetirizine			
Jobst 1994 Germany, The Netherlands (Fair)	Symptoms were scored every day by the patient and recorded on a diary card according to a 4-point scale of main rhinitis symptoms (sneezing, nasal discharge, and nasal obstruction), and of accessory rhinitis symptoms (nasal pruritus and ocular pruritus): 0=not present at all, 1=mild, 2=moderate, 3=severe. At each visit (baseline, 1 week, 2 weeks) assessments were conducted by the investigator (5 point scale, 0= worsening, 4=excellent improvement) and diary cards were collected.	NR/NR/330	17/0/311; reasons for withdrawal: incomplete information (1), lack of efficacy (4), AE (8), development of an exclusion criteria (1), use of unauthorized medication (1), unrelated to study (2)
Loratadine			
Yang 2001 Taiwan (Fair)	Evaluations at baseline, day 7, and day 21 during which investigators reevaluated the 5 cardinal symptoms of allergic rhinitis. Parents were given diary cards for daily recording of the 5 symptoms. All symptoms were graded on a 4-point scale: 0=absent, 3=severe.		NR/NR/46

Evidence Table 11. Perennial allergic rhinitis trials in children

Author Year Country Quality Score	Results
Placebo-controlled trials	
Cetirizine	
Jobst 1994 Germany, The Netherlands (Fair)	Compliance: Considering patient's severest symptom: % days asymptomatic: C3>P (p=0.008), NSD C1 vs P and C2 vs P % days when symptoms were absent or mild: C3>D (p=0.016), NSD C1 vs P and C2 vs P % days when no severe symptoms: C1>P (p=0.012), B>P (p=0.006), C3>P (p=0.002) Over time patient's severest symptom score decreased in all groups, most marked for C3, least marked for P Investigator assigned severest symptom scores: among-group differences week 1 (p=0.022), week 2 (p=0.052), P had highest score; NSD among C1, C2 and C3 at end week 2 Investigator global assessment score (end week 2): differences among groups (p<0.0001), little difference between C2 and C3
Loratadine	
Yang 2001 Taiwan (Fair)	Mean percentage change from baseline (L vs P; p-values are for the between-group comparison at each time point) <u>Investigator-assessed TSS:</u> Day 7 (visit II): 48.9% vs 14.8% (p=0.003) Day 21 (visit III): 42.2% vs 22.7% (p=0.063) <u>Patient-assessed TSS:</u> Week 2: 4.6% vs 2.8% (p=0.029) Week 3: 13.2% vs 5.6% (p=0.014) Individual symptoms: Rhinorrhea (p=.009) and sneezing (p=004) improved in L vs P; other symptoms NSD

Evidence Table 12. Quality assessment perennial allergic rhinitis trials in children

Internal Validity

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Baelde et al, 1992 Belgium	Yes	Method not reported	Yes	Yes	Yes; described as 'double blind' but unclear who	Yes	Yes
Ciprandi et al, 2001 Italy	Method NR	Method not reported	Yes (no statistics)	Yes	Yes; described as 'double blind' but unclear who	Yes	Yes
Ciprandi et al, 2004 Italy	Method NR	Method NR	Nasal characteristics similar between groups; no other information	Yes, but little detail	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded
Hseih 2004 Taiwan	Yes	Method NR	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes
Jobst et al, 1994 Germany, The Netherlands	Yes	Method not reported	Yes	Yes	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded
Lai 2002 Taiwan	Yes	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Pearlman et al, 1997, Winder et al, 1996 (safety) US	Method not reported	Not reported	Difference in systolic blood pressure (no data), otherwise similar.	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessment perennial allergic rhinitis trials in children

Author Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Baelde et al, 1992 Belgium	Attrition and adherence yes, contamination no.	No (13/138)	No: 125/138 analyzed; also subjects withdrawn for protocol violations	Yes, 4/138 either dropped out or withdrawn as deviated from protocol	NR, affiliation of authors is UCB Pharma Sector (Research and development), Braine-l'Alleud, Belgium	Fair
Ciprandi et al, 2001 Italy	Attrition and adherence yes, contamination no.	Attrition 0	Yes	No	NR	Fair
Ciprandi et al, 2004 Italy	None reported	NR	Unclear; insufficient information	NR	NR	Poor: no information on attrition or baseline comparability
Hseih 2004 Taiwan	Exclusions 4 for lack of data at follow-up, attrition 1 for lack of efficacy; cross-overs NR	No	No, 60/65 analyzed; no mention cross-overs	Yes, 4 excluded as TSS not performed during treatment period	NR	Fair
Jobst et al, 1994 Germany, The Netherlands	Attrition and compliance yes, contamination no	No	No (328/330 analyzed)	One patient withdrawn for protocol violation	NR; senior author (H van deVenne) affiliated with UCB, Pharma Sector, research and Development, Belgium	Fair
Lai 2002 Taiwan	Attrition reported (4/80); incomplete baseline data (7/80)	No	No; 69/80 analyzed; no mention cross-overs	Yes, 7/80 patients excluded because no TSS recorded during treatment period	Research grant of Chung Shan Medical University	Fair
Pearlman et al, 1997, Winder et al, 1996 (safety) US	Yes.	No.	No (205/209 analyzed)	No.		Fair

Evidence Table 12. Quality assessment perennial allergic rhinitis trials in children

	External Validity				
Author Year Country	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Relevance**
Baelde et al, 1992 Belgium	NR/NR/138	If excluded drugs had been taken prior to study, then washout periods of up to 2 weeks	NR	NR	Unclear
Ciprandi et al, 2001 Italy	NR/NR/20	None	NR	NR	Unclear
Ciprandi et al, 2004 Italy	NR/NR/20	NR	NR	NR	Unclear
Hseih 2004 Taiwan	NR/NR/65	For 7 days prior to study patients could not use any H1 antagonist, decongestant, or any form of steroid.	NR	NR	Unclear
Jobst et al, 1994 Germany, The Netherlands	NR/NR/330	Washout	NR	NR	Unclear
Lai 2002 Taiwan	NR/NR/80	NR/ for 7d prior to study, patients could not use an H1-antagonist nor any form of steroid or decongestant	NR	NR	Unclear
Pearlman et al, 1997, Winder et al, 1996 (safety) US					

Evidence Table 12. Quality assessment perennial allergic rhinitis trials in children

Internal Validity

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Sienra-Monge 1999 Mexico	Method NR	Method NR	Weight higher in loratadine group (18.1 vs 16.3 kg, p<0.05)	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes
Sienra-Monge et al, 1999 Mexico	Method not reported	Method not reported	Weight higher in loratadine group, otherwise similar	Yes	Unclear; reported as "double blind"	Unclear; reported as "double blind"	Unclear; reported as "double blind"
Yang et al, 2001 Taiwan	Method not reported	Method not reported	Yes	Yes	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded	Study described as 'double blind' but unclear who was blinded

Evidence Table 12. Quality assessment perennial allergic rhinitis trials in children

Author Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
Sienra-Monge 1999 Mexico	Attrition (2/80, both in group A)	No (2.5%)	No, 2 cetirizine patients withdrew due to AEs, not analyzed	No	Glaxo/Welcome Mexico	Fair
Sienra-Monge et al, 1999 Mexico	Attrition yes, others no	No	No (2/80 not analyzed). Did not analyze patients who experienced adverse effects (considered treatment failures)	No	Glaxo/Welcome Mexico SA de CV, Col San Lorenzo Huipulco, Mexico	Fair
Yang et al, 2001 Taiwan	Attrition and adherence yes, contamination no	High (23%) withdrew, but NSD between groups	No (46/60 analyzed)	No	Schering-Plough	Fair

Evidence Table 12. Quality assessment perennial allergic rhinitis trials in children

	External Validity				
Author Year Country	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Relevance**
Sienra-Monge 1999 Mexico	NR/NR/80	None; none	NR	NR	Unclear
Sienra-Monge et al, 1999 Mexico	NR/NR/80	No/no	NR	NR	Unclear
Yang et al, 2001 Taiwan	NR/NR/60	Evaluations at baseline, day 7, and day 21 during which investigators reevaluated the 5 cardinal symptoms of allergic rhinitis. Parents were given diary cards for daily recording of the 5 symptoms.	NR	NR	Unclear

Evidence Table 13. Urticaria trials in children

Author Year Country (Quality Rating)	Study Design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ethnicity
Active-controlled trials				
La Rosa 2001 Italy Fair	RCT, active control Double blind Parallel group Multicenter	CIU Children 2-6 years with CIU for ≥ 6 weeks with ≥ 3 instances of recurrence of acute urticaria at separate weekly intervals; ≥ 3 of 4 urticaria-related symptoms: itching, erythema, papules, or edema and minimum symptom score; weight ≥ 11 kg	Hepatic or renal disease, Quincke edema, active infection, corticosteroid dependence, no adherence to washout period, hypersensitivity to piperazine or paraben	Mean age: 3.85y Range: 2-6y 61.3% male Ethnicity: NR
Placebo-controlled trials				
Simons 2001, Simons 1999 Europe and Canada ETAC study Fair	RCT, placebo-controlled Double blind Parallel group Multicenter	Prevention of acute urticaria in children with atopic dermatitis Children 12-24 months old with atopic dermatitis but no asthma or other systemic disorder and who had at least one allergic parent or sibling. Is the Early Treatment of the Atopic child (ETAC) study.	Asthma, any other persistent or recurrent pulmonary disease, other systemic disorder, history of neonatal distress, sleep apnea in subject or siblings, need for immune-modulating medications or immunotherapy, adverse reaction to cetirizine or other H1-agonists, weight <3rd percentile, abnormality of the QTc interval on ECG	Mean age: 16.8m in A, 17.2m in B; range: 12-24m 62 % male Ethnicity: NR

Evidence Table 13. Urticaria trials in children

Author Year Country (Quality Rating)	Interventions	Allowed other medications/ interventions
Active-controlled trials		
La Rosa 2001 Italy Fair	C: Cetirizine: 5 mg qd (n=31) O: Oxatomide: 25 mg qd (n=31)	No
Placebo-controlled tria		
Simons 2001, Simons 1999 Europe and Canada ETAC study Fair	C: Certirizine 0.25 mg/kg bid; (range: 5-11 mg /d) P: Placebo bid Treatment for 18 months and then patients were followed for 6 months after treatment stopped. Goal of treatment was to prevent acute urticaria in young children with atopic dermatitis.	Yes

Evidence Table 13. Urticaria trials in children

Author Year Country (Quality Rating)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Active-controlled trials			
La Rosa 2001 Italy Fair	Symptom scale: 0 = absence of symptoms, 1 = slight symptoms present but not annoying, 2 = moderated symptoms that were annoying but not severe enough to hinder daily activity or sleep, 3 = symptoms severe enough to hinder daily activity or sleep Parent's rating of child's health: 100 mm VAS; 0 = totally unsatisfactory condition to 100 = totally satisfactory condition Investigator's assessment of treatment results; 0 = lack of result, 1 = satisfactory result, 2 = good result, 3 = optimal result Assessments at Day 0 (baseline), Day 14, and Day 28	NR/ NR/ 62	5/ NR/ 57
Placebo-controlled tria			
Simons 2001, Simons 1999 Europe and Canada ETAC study Fair	Parent/primary caregiver used a diary card to record all symptoms, events, and medications on a weekly basis when child was well and on a daily basis when child had symptoms	NR/NR/817	26/73/797 at 18m, 694 at 24m

Evidence Table 13. Urticaria trials in children

Author Year Country (Quality Rating)	Results
Active-controlled trials	
La Rosa 2001 Italy Fair	Change in VAS parents' score from Days 0 to 14, C vs O +39mm vs +34 mm, NSD between groups Change in VAS parents' score from Days 0 to 28, C vs O: +62mm vs +57mm, NSD between groups Investigators' mean symptom score (sum of individual symptom scores): progressive reduction in scores in both C and O; NSD between groups Change in score from baseline at Day 14: -51 vs -51 points, NSD Change in score from baseline at Day 28: - 58 vs -58 points, NSD *(data estimated from graph)* Clinical evaluation by investigators at end of study, C vs. O: Excellent: 33.3 vs 20.7%, NSD Good: 53,3% vs 69.0%, NSD Moderate: 13.4 % vs 6.9%, NSD Bad: 0% vs 3.4%, NSD
Placebo-controlled tria	
Simons 2001, Simons 1999 Europe and Canada ETAC study Fair	In total study population over 18m treatment period, 87 children had 138 urticaria episodes; 66 had 1 episode, 10 had 2 episodes, and 11 had 3 -10 episodes. % with urticaria episodes during 18-month treatment, C vs P: 5.8% vs 16.2%, p<0.001 % with urticaria episodes during 6-month follow-up (after treatment stopped), C vs P: 3.4% vs 5.2% , NSD

Evidence Table 14. Quality assessment of urticaria trials in children

Internal Validity

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
La Rosa	Yes	Method not reported	Yes for age, sex, height-data not reported, other characteristics not reported	Yes	States "double-blind" but not specified	States "double-blind" but not specified	Yes
Simons 2001, Simons 1999	Yes	Yes	Yes for age; others NR	Yes	States "double-blind" but not specified; AE reviewed by blinded observer	States "double-blind" but not specified	Yes

Evidence Table 14. Quality assessment of urticaria trials in children

Author Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
La Rosa	Attrition reported (5/62)	No	No, 57/62 analyzed; no mention cross-overs	No	UCB Laboratories, Pianezza, Torino, Italy	Fair
Simons 2001, Simons 1999	Attrition reported, others not	No; 12% over 18 months, no differential	No; attrition 99/817	NR	UCB, SA (Belgium)	Fair

Evidence Table 14. Quality assessment of urticaria trials in children

External Validity

Author Year Country	Number screened/ eligible/ enrolled	Run-in/ Washout	Class naïve patients only	Control group standard of care	Relevance
La Rosa	NR/NR/62	NR/ 4-d washout, or 14-d washout if patients had been treated with ketotifen or corticosteroids	NR	NR	Unclear
Simons 2001, Simons 1999	NR/NR/817	None; None	NR	NR	Young children (12-24 months)

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

Author, Year	Study Outcomes, Characteristics	Results
Bender 2003	Sedation, performance impairment First and second generation antihistamines, meta-analysis of trials of diphenhydramine vs. astemizole, ACR, cetirizine, fexofenadine, loratadine, terfenadine. Inclusion: 18 trials of allergy, randomized, double-blind, placebo controlled, sedation scores, English, with means and variances, vs. diphenhydramine (mostly healthy patients. or < 2 wks). Exclusion: Non-allergic, no sedation measures, no measure of variance.	Sedation effect size small and variable among trials, however diphenhydramine significantly worse vs. placebo: 0.36 (95% CI 0.20-0.51, p=0.0001; diphenhydramine significantly worse vs. second generation antihistamines: 0.31 (95% CI 0.17-0.45, p=0.0001) Second generation antihistamines significantly worse vs. placebo: 0.14 (95% CI 0.01-0.26, p=0.030)
Craig-McFeely 2001	Fexofenadine in UK prescription event monitoring cohort. Inclusion: Survey GPs with rxs Mar -Aug '97. Baseline 59% female, ages 36-39, AR 55%, CIU 4.3% (28.4% NR). Cohort 16,638 patients.	AE total: 40 (0.2%) in 27 patients, d/c <2%, 30 unrelated deaths. Cardiac: 8 non-serious, 1 irregular pulse w/ possible grapefruit drug/food interaction. Other possible: 1 aggression, 1 neutropenia, resolved with d/c. Pregnancy-related: 47 total, of 30 exposed 1st trimester, 4 miscarriages, 1 therapeutic termination, 1 PE death, 1 unknown, 23 live births with 3 unrelated AE: premature/incompetent cervix, positional foot deformity and fetal distress
de Abajo 1999	Cardiac Ventricular arrythmia and AH ACR, astemizole, cetirizine, loratadine, terfenadine, UK cohort. Inclusion: Patients <80 yrs, rx Jan '92-Sept.'96, 5 years. Exclusion: cancer, arrhythmias Baseline: Cohort 197,425 with 2.6 rx/patient, 151events identified, 86 reviewed.	Arrythmia results: Total idiopathic (none fatal) 18 cases Any antihistamine: 9 cases (7 in 1st month); 1.9 per 10,000 person-years (95% CI 1.0-3.6), 4.2 times higher than non-use (95% CI 1.5-11.8). Second generation antihistamines- 1 case in 57,000 rxs, astemizole highest RR 19 (95% CI 4.8-76) cetirizine RR 7.9, (95% CI 1.6-39.3), loratadine RR 3.2 (CI NS) terfenadine RR 2.1 .(CI NS) No interactions with P450Is (low ketoconazole use).

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

	Internal Validity						
Author, Year	**Non-biased selection?**	**Low overall loss to follow-up?**	**Adverse events pre-specified and defined?**	**Ascertainment techniques adequately described?**	**Non-biased and adequate ascertainment methods?**	**Statistical analysis of potential confounders?**	**Adequate duration of follow-up?**
Bender 2003	Yes	N/A	Yes	Yes	Yes	Yes	Yes
Craig-McFeely 2001	N/A	8.7% non-evaluable forms	Yes	Yes	Yes	Yes	Yes
de Abajo 1999	Yes	Yes low loss to f/u 5% missing	Yes	Yes	Yes	Yes	Yes f/u 5 years

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

	External Validity					
Author, Year	**Adequate description of population?**	**Groups similar at baseline?**	**# screened / eligible / enrolled?**	**Exclusion criteria specified?**	**Funding**	**Overall Quality**
Bender 2003	Yes	Yes	Yes, # studies	Yes	NR	Fair
Craig-McFeely 2001	Yes	Yes	Identified 35,817 rxs from 8057 GPs, 18,238 (50.9%) returned.	N/A	Public funding	Fair
de Abajo 1999	Yes	Yes	Yes, screened 3 million	Yes: 60 excluded for non-confirmed diagnosis	Public funding	Fair

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

Author, Year	Study Outcomes, Characteristics	Results
Finkle 2002	Serious injury Diphenhydramine or loratadine at 1 month; cohort. Inclusion: Health care claims database Jan '91-Dec.'98. Baseline: diphenhydramine 12,106 pts; loratadine 24, 968 pts; ages 49-55, 53.1%-55.9% female. NS injury rates same time previous year	Diphenhydramine 308 injuries per 1000 patient years vs.137 in loratadine, age and gender adjusted RR 2.27 (95% CI 1.93, 2.66).
Lal 2000	Blood glucose Randomized, double-blind, placebo-controlled. Cetirizine 10mg qd, loratadine 10mg qd, clemastine 1mg bid. Inclusion: AR, Jan-Nov '97. Exclusion: Diabetes mellitus, cardiac, liver, renal, respiratory disease. Baseline: Similar; ages 31-33 yrs (age? 10-yr-old in clemastine), 58.3% male (usually more females), fasting blood glucose 78.2-81.33 g%, ppg 97.11-101.50 g%. G	Glucose: cetirizine >ppg p=0.02, loratadine NS difference clemastine NS difference
Mann 2000	Sedation Loratadine vs cetirizine, fexofenadine, acrivastine, PEM UK cohort. Inclusion: May-Aug '89 cetirizine and loratadine, Mar-Aug '97 fexofenadine Baseline: 43,363 pts, 56%-62% female, 36%-49% <30yrs , 7-14% >60yrs.	Sedation vs. loratadine: significantly higher for cetirizine (odds ratio 3.52, 95% CI 2.17 to 5.71, p<0.0001), NS difference for fexofenadine (odds ratio 0.63 (95% CI 0.36-1.11, p=0.1); overall sedation was low with no correlation with accident or injury.

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

	Internal Validity						
Author, Year	**Non-biased selection?**	**Low overall loss to follow-up?**	**Adverse events pre-specified and defined?**	**Ascertainment techniques adequately described?**	**Non-biased and adequate ascertainment methods?**	**Statistical analysis of potential confounders?**	**Adequate duration of follow-up?**
Finkle 2002	N/A	N/A	Yes	Yes	Yes	NR	Yes
Lal 2000	Yes	10% d/c, 1 cetirizine 3 loratadine	No events	Yes	Yes	NR	No, f/u only 1 week
Mann 2000	N/A	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

	External Validity					
Author, Year	**Adequate description of population?**	**Groups similar at baseline?**	**# screened / eligible / enrolled?**	**Exclusion criteria specified?**	**Funding**	**Overall Quality**
Finkle 2002	Yes	Yes	NR	N/A	manufacturer funded	Fair
Lal 2000	Yes	No	NR	Yes	NR	Poor
Mann 2000	Yes	Yes	51%-57% response rate	N/A	Public funding	Fair

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

Author, Year	Study Outcomes, Characteristics	Results
Salmun 2000	Somnolence and motivation Randomized, double-blind trial assessing VAS scale 1-10 in workday with loratadine 10mg qd, cetirizine 10mg qd for 1 week. Inclusion: AR symptoms 2-3 on 0-3 scale, positive skin test wheal 3mm > control or intradermal administration wheal 7mm >control in past year, age ≥12. Exclusion: Interfering disease, asthma requiring steroids, sinusitis or URI, rebound rhinitis, past >2 ADEs or AE to antihistamines, pregnant/lactating. Baseline: 60 pts, ages 31.2 -32.6 yrs, 52% men, similar scores except cetirizine patients. Baseline 20% difference in somnolence.	Significantly more somnolence and less motivation with cetirizine vs. loratadine at 10 am, noon, and 3 pm. Other AEs NS difference

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

	Internal Validity						
Author, Year	**Non-biased selection?**	**Low overall loss to follow-up?**	**Adverse events pre-specified and defined?**	**Ascertainment techniques adequately described?**	**Non-biased and adequate ascertainment methods?**	**Statistical analysis of potential confounders?**	**Adequate duration of follow-up?**
Salmun 2000	Yes	Yes	Yes	Yes	Yes	NR	Short f/u 1 week

Evidence Table 15. Adverse events in systematic review and observational studies (from original report)

	External Validity					
Author, Year	**Adequate description of population?**	**Groups similar at baseline?**	**# screened / eligible / enrolled?**	**Exclusion criteria specified?**	**Funding**	**Overall Quality**
Salmun 2000	Yes	Yes	NR, 60 patients enrolled	Yes	manufacturer funded	Fair-poor

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Method and timing of assessing adverse events	Adverse Events
Seasonal allergic rhinitis		
Berger 2003	Patients were seen on an outpatient basis on days .7, 1, 7, and 14. A diary card in which to record symptom severity was given on day -7.	Most common AEs per treatment: Bitter taste: 11% azelastine, 4% azelastine + loratadine Headache: desloratadine 3%, placebo 7%4% Pharyngitis: desloratadine 4: Somnolence: desloratadine 1%, azelastine 2%, azelastine + loratadine 1%, placebo 1%
Bernstein 2004 USA	Pt evaluated AEs from daily diary cards and investigator rated AEs at clinic visits	All AEs data given as loratadine 10 mg vs fluticasone spray vs placebo Incidence of AEs: 42% vs 44% vs 40% Headache: 18% vs 17% vs 12% Discontinuation due to AEs: 4% vs 3% vs 2%
Ciprandi 1997 Italy	NR	No significant AEs reported.
Corren 2005 USA	Tolerability assessed in terms of AEs and vital signs, and heart and respiration rates, all of which were measure at baseline and at end of study.	<u>Most common AEs, with ≥ 1% pts reporting these, cetirizine 10 mg vs azelastine spray:</u> Bitter taste: <1% vs 3.3% Epitasis: <1% vs 2.0% Somnolence: 2.6% vs 1.3% Nasal discomfort: <1% vs 1.3% Discontinuation due to AEs: 2 cetrizine pt (1 each: somnolence and skin rash) vs 4 azelastine patients (1 each: sleeplessness, sinus infection, nausea, and allergy exacerbation)

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Total withdrawals; withdrawals due to adverse events	Internal Validity: Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Seasonal allergic								
Berger 2003	Withdrawals for AEs Azelastine : 2 patients (moderate chest pain; lightheadedness) Desloratadine: 1 patient (headache and nausea) Placebo: 1 patient (rash)	No	Yes	No	No	NR	No	Yes
Bernstein 2004 USA	Total withdrawals: 13% from loratadine, 6% from fluticasone, 9% from placebo; discontinuation due to AEs: 4% vs 3% vs 2%	Unclear, methods NR	Yes	No	No	Unclear	NR	Yes (4 weeks)
Ciprandi 1997 Italy	0 / 0	Yes	Yes	Yes	Yes, diary	Yes	NR	Yes, all patients completed
Corren 2005 USA	8; 6 (2 in cetirizine, 4 in azelastine)	Unclear, methods NR	Yes	No	Yes	Unclear	NR	Yes (2 weeks)

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Method and timing of assessing adverse events	Adverse Events
Dockhorn 1987	Pts recorded daily severity of symptoms and other relevant comments in diary. These were returned on days 3, 7 and 14 of treatment for investigator evaluation of efficacy and safety. Blood pressure, body temperature, pulse and respiration rate determinations were repeated at clinical visits while clinical laboratory tests, ECG, and body weight were repeated at study completion. Any clinically meaningful changes from baseline were noted. In addition, AEs were elicited at each visit. Date, time of onset and duration of any AE were recorded and severity of any AE was graded as mild, moderate or severe by standard definition.	More AEs (considered probably or possibly treatment-related) in clemastine 2mg group: clemastine 2mg 37%, loratadine 10mg 21%, placebo 20% (p<0.01) Sedation: clemastine 22% vs loratadine 6% (p<0.01) D/C treatment: NR
Hampel 2003 USA	Pts recorded AEs in daily and symptoms were evaluated at each study visit; pts asked to self-evaluate drowsiness and motivation daily at 7am, 10am, and 3pm using a VAS (0-100, with 100= extremely sleepy or not motivated at all).	16.8% AEs observed: 16.8%: fexofenadine 16.9%, cetirizine 16.6% 4.4% drug related AEs: 4.0% fexofenadine, 4.8% cetirizine No serious AEs reported Drowsiness: significantly greater with fexofenadine than with cetirizine (p=0.0110) Overall change from baseline in drowsiness correlated with the change from baseline in motivation D/C treatment: 16 (7 fexofenadine 180mg vs 9 cetirizine 10mg); 6 of 16 due to AEs

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Total withdrawals; withdrawals due to adverse events	Internal Validity: Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Dockhorn 1987	NR; NR	Yes	Yes	No	Yes	Yes	No	Yes
Hampel 2003 USA	total withdrawals=16; 6/16 for AEs	Yes	Yes	Yes	Yes, diary	Yes	NR	Yes

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Method and timing of assessing adverse events	Adverse Events
Hampel 2004 USA	Pts were provided with a daily diary card, recording took place every morning and evening, pts recorded any AEs throughout the study period.	223 pts (29.8% report 410 AEs; NSD between study groups in # of pts who reported ≥ 1 AE. *Data on AEs given as loratadine 10mg vs ebastine 10 mg vs ebastine 20 mg vs placebo* AEs related to body as whole system: 15.3% vs 11.2% vs 11.8% AEs associated with respiratory system: 12.2% vs 8.5% vs 7.5% vs 10.2% (72 pts (9.6%) reported 101 respiratory system AEs; all unrelated to study drug) Headache: 5.8% vs 4.3% vs 3.2% vs 4.3% Dyspepsia: 0% vs 0% vs 3.2% vs 0% Pharyngitis: 0% vs 0% vs 0% vs 4.3% Serious AEs: 8 pts vs 14pts vs 5 pts vs 13 pts No deaths reported Prolonged QTc intervals: 1.6% vs 3.2% vs 2.2% vs 0.5% (all mild and none resulted in discontinuation) Slight increase in heart rate for all 4 treatment groups; 1 report of palpitation in a Loratadine pt. CNS AEs: 33 (4.4%) of pts reported 44 CNS AEs Somnolence: 0 vs 1.6% vs 3.2% vs 0%
Howarth 1999 UK, US, France	AEs recorded daily along with symptoms; pts self-assessed somnolence on VAS every evening before bed. Blood samples taken at baseline and end of study	Treatment-related AEs: fexofenadine 120mg 23%; fexofenadine 180mg 23%; cetirizine 10mg 25%; placebo: 25%; D/C treatment: 117 (14% of total), similar among groups (numbers per group not reported)
Martinez-Cocera 2005 Spain	AEs reported by pts or observed by investigators	Data given as cetirizine 10 mg vs rupatadine 10 mg Related (possible, probable, or definite) AEs: 42.7% vs 39.5%, NSD headache: 19.7% vs 15.3%, NSD fatigue/asthenia: 6.8% vs 10.5%, NSD somnolence: 8.5% vs 9.6%, NSD

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Total withdrawals; withdrawals due to adverse events	Internal Validity: Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Hampel 2004 USA	100 pts ; 20 pts (2.7%)	Unclear, methods NR	13%	No	No	Unclear	Baseline variables used as covariates in analyses	Yes (4 weeks)
Howarth 1999 UK, US, France	22 pts; 13 pts Withdrawals for AEs by group: placebo - 2%, 2% for both groups of fexofenadine combined, and <1% for cetirizine	Yes	Yes	Yes	Yes	Yes	No	NR
Martinez-Cocera 2005 Spain	37/12	Unclear, methods NR	No (15%)	No	No	Unclear	Yes	Yes (2 weeks)

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Method and timing of assessing adverse events	Adverse Events
Okubo 2004, 2005 Japan	Any unfavorable signs and symptoms observed during the period of administration of the study drug were classified as AEs. Safety items included data obtained and symptoms experienced during the study period. AEs described in the allergy diary were not reported; only those reported at physician's examinations	No serious adverse events were reported. There was no significant difference in the number of adverse events between the two groups (P= 0.568). A high white blood cell count and headache occurred most frequently.
Prenner 2000 USA	NR	Adverse events: 22.1% of fexofenadine 120mg and 18.2% of loratadine 10mg group had ≥ 1 adverse events. AEs considered treatment related in 8.3% of fexofenadine 120mg, 5.3% of loratadine 10mg Discontinued treatment: NR Discontinued due to AEs: NR
Ratner 2004 USA	Patients recorded any AEs; these were classified and summarized.	No significant difference among the three groups in % of pts who reported >1 AEs: 29.4% ebastine, 33.3% loratadine, 25.4% placebo Total number of AEs reported: 146 ebastine, 138 loratadine, 53 placebo 89.9% of AEs mild or moderate intensity, 10.1% severe (most unrelated to treatment) Headache (reported by >2 loratadine pts) Nervous system: ebastine 4.6%, no clinically significant trends Digestive system: 3.2% ebastine, 3.5% placebo, no clinically significant trends Cardiovascular system: 2.8% ebastine, 2.5% loratadine, 4.2% placebo Prolonged QTc interval was the most frequently cardiovascular AE: 3.9% ebastine, 3.6% loratadine, 5.6% placebo; all increases in QTc were mild w/o resulting in discontinuation of treatment. Discontinued treatment: 85 Discontinued due to AEs: 18 (3.2% ebastine, 2.2% loratadine, 2.1% placebo)

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Total withdrawals; withdrawals due to adverse events	Internal Validity: Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Okubo 2004, 2005 Japan	3/NR	Unclear, methods NR	Yes (3/210)	No	No	Unclear; AEs recorded in patients' diaries were not recorded in study	Yes	Yes (2 weeks)
Prenner 2000 USA	NR; NR	Yes	Yes	No	No	Yes	No	Yes
Ratner 2004 USA	18 patients (2.6%) withdrew due to AEs	Unclear; no data on selection of patients	85/703 (12.5%)	No	Yes	Unclear; blinding of assessor NR	Yes, baseline groups differed on duration of allergy symptoms; baseline factors used as covariates	Yes (4 weeks)

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Method and timing of assessing adverse events	Adverse Events
Saint-Martin 2004 France	Patients reported AEs in daily diary; no other details. Reported to investigators day 7 and 14	Patients reporting at least 1 AE: rupatadine 10mg 64.9%; rupatadine 20mg 53.6%; loratadine 10mg 49.1%; NSD among groups; headache most frequent AE; others; somnolence, asthenia, coughing. Only significant difference was somnolence between rupatadine 10mg vs rupatadine 20mg and rupatadine 10mg vs loratadine 10mg. Other AEs with incidence rate <5%: back pain, dry mouth, pharyngitis (NSD among groups)
van Adelsberg 2003 USA	Safety and tolerability were assessed by adverse events monitoring, physical examinations, and laboratory testing	Loratadine=montelukast for discontinuations because of AEs. There were no clinically meaningful differences between treatment groups in the incidence of clinical or laboratory adverse experiences. 1 withdrawal for clinical adverse experience in loratadine group, reason NR
van Cauwenberge 2000 Europe and South Africa	AEs assessed at each visit at each week of study, and were contacted 7 d after study to find out if AEs had occurred after treatment.	AE data given as loratadine 10mg vs fexofenadine 120mg vs placebo AEs: 16.4% of total AEs by group: 17.5% vs 16.8% vs 14.7% D/C treatment: 10% of total D/C treatment by group: 12% vs 9% vs 11%

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Total withdrawals; withdrawals due to adverse events	Internal Validity: Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Saint-Martin 2004 France	Overall 11 patients (3.2%); rupatadine 10mg 4 patients, rupatadine 20mg 5 patients, loratadine 2 patients; NSD among groups.	Unclear, methods NR	No, 65+19 lost to follow-up	No	No	Unclear	Yes, center and basal SS used as covariates	Yes (2 weeks)
van Adelsberg 2003 USA	79; 1 withdrawal in loratadine group for clinical AE, 0 for laboratory AE Montelukast = 11 withdrawals dues to clinical AEs Placebo = 14 due to clinical AEs and 1 due to lab AEs	Unclear, methods NR	Yes	No	No	Unclear	No	Yes (4 weeks)
van Cauwenberge 2000 Europe and South Africa	71; 15	Yes	Yes	No	Yes	No	No	Yes

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Method and timing of assessing adverse events	Adverse Events
Urticaria		
Breneman 1996	Clinical lab tests performed at baseline and at end of study. All AEs were volunteered or observed and recorded at day 1, at the ends of weeks1, 2, 3, and 4.	Sedation significantly different hydroxyzine 75mg vs placebo p=0.001 D/C for somnolence: cetirizine 10mg 1 pt, hydroxyzine 75mg 4 pts, placebo 1 pt. 3 more placebo pts discontinued.
Guerra 1994 Italy	Pts seen at 3, 7, 14, and 28 d after treatment start when evaluations were made of clinical symptoms and any side effects	NS difference in Total AEs: Loratadine 15.8%, cetirizine 27.5%, placebo 15.8%. One cetirizine patient withdrew due to gastralgia.
Handa, 2004 India	Patients self-report AEs; no details provided	Cetirizine 10 mg: drowsiness: 7.7%, constipation: 5.8%, epigastric pain: 3.8%, cough: 3.8% Fexofenadine 180mg: drowsiness: 4.5%, and 2.2% reported headache, feet swelling and abdominal pain. NSD between groups (p=0.291)
Kaplan, 2005 USA	Patient-reported AE; 12-lead ECG; clinical lab tests at baseline and final visit	Safety evaluation population = 259 (167 in fexofenadine vs 92 in placebo) Treatment-associated AEs: fexofenadine 180mg 31% vs placebo 37%, NSD Total headache: fexofenadine 180mg 5%, placebo 3% Headache related to study drug: fexofenadine 180mg 2%, placebo 0% Serious AEs: 1 patient in group fexofenadine 180mg had asthma requiring hospitalization; no considered related to the study drug "No clinically relevant changes from baseline to end of treatment seen in clinical laboratory data, vital signs, or ECGs"
Monroe, 2003 International	Vital signs recorded at all visits, ECGs and laboratory tests performed at screening and visit 7. All AEs were recorded and graded for severity and potential relation to study medication. Safety evaluations included the incidence of treatment-emergent AEs, discontinuations due to AEs, and changed from baseline in vital signs, laboratory parameters, and ECG intervals.	Overall AE profile of desloratadine was similar to placebo (data not reported).

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Total withdrawals; withdrawals due to adverse events	Internal Validity: Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Urticaria								
Breneman 1996	43; 3	Yes	Yes	Yes	Yes, diary	Yes	NR	Yes
Guerra 1994 Italy	NR ; 1 pt withdrew due to AEs	Yes	No	Yes	NR	Yes	NR	Yes
Handa, 2004 India	19; NR	Unclear, methods NR	No; 19/116 left the study (16%)	No	No	Unclear if assessor blinded and how AEs elicited	NR	Yes (2 weeks)
Kaplan, 2005 USA	25; NR	See QA table	See QA table	See QA table	See QA table	See QA table	See QA table	See QA table
Monroe, 2003 International	Total: 16.4% desloratadine vs 31.8% placebo; Due to AEs: 3 desloratadine, vs 2 placebo	Yes	Yes	No	Yes	Yes	Yes (RCT)	Yes (6 weeks)

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Method and timing of assessing adverse events	Adverse Events
Perennial allergic rhinits		
Frolund 1990	AEs obtained by asking the same general question at each evaluation; details recorded by clinician. Lab test done at baseline and endpoint; lab test with abnormal results were repeated.	AEs significantly less with loratadine 10mg than clemastine 1mg or placebo ($p<0.05$). AE of sedation significant with clemastine 1mg. loratadine 10 mg qd: 8/53 AEs. 5 d/c not from AE clemastine 1 mg: 30/51 AEs, d/c, 1 AE and 2 failures. placebo: 13 d/c, 9 due to failures
Simons 2003 US and Canada	Vital signs and AEs assessed at each study visit. All AEs graded according to severity and the potential relationship to study medication. Blood chemistry and hematology tests, urinalysis, and 12-lead ECGs with reporting of ventricular rate and PR, QRS, QT, and QTc intervals were performed at screening and end of study;	Incidence of treatment emergent AEs (desloratadine vs placebo): Overall: 25.8% vs 31.6% Headache: 7.4% vs 7.1% Infection, viral: 3.3% vs 5.3% Pharyngitis: 3.0% vs 1.5% URTI: 2.7% vs 2.7% Dry mouth: 2.4% vs 1.8% No clinically significant differences in vital signs, clinical laboratory test results, or ECGs, including QTc intervals compared with baseline or between groups.

Evidence Table 16. Adverse events from efficacy trials in adults

Author, year country	Total withdrawals; withdrawals due to adverse events	Internal Validity						
		Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Perennial allergic								
Frolund 1990	25 pts; 1 pt	Yes	Yes	Yes	Yes, diary	Yes	NR	Yes
Simons 2003 US and Canada	Total: 5.93% desloratadine vs 6.48% placebo Due to AEs: 3.3% desloratadine vs 2.1% placebo (NSD)	Yes	Yes	No, except for ECG results	Yes	Yes	Yes (RCT)	Yes (4 weeks)

Evidence Table 17. Adverse events in other study designs in adults

Author Year Quality Score	Study Design Setting	Population Eligibility criteria	Exclusion criteria
CDC 2004 Fair	Case-control, from national Birth Defects Prevention Study: a multi state study of environmental and genetic risk factors for major birth defects	Infants identified through birth defect surveillance systems in 8 states; mothers interviewed by telephone. For this analysis, case population was male infants with second or third degree hypospadias; control population is live-born male infants with no major birth defects selected at random from the same populations as the case group. Exposure was defined as any maternal use of loratadine from 1m before pregnancy through the first trimester.	If data were incomplete patients were excluded

Evidence Table 17. Adverse events in other study designs in adults

Author Year Quality Score	Age Gender Race/ethnicity	Interventions	Allowed other medications/ interventions	Method of AE assessment and timing of assessment	Adverse Events
CDC 2004 Fair	All infants were identified just after birth 100% male	NA	Exposure to other antihistamines was controlled for	At birth, by provider and reported to surveillance system	OR of hypospadias with loratadine exposure: 1.29 (0.62-2.68); use of nonsedating antihistamines, including loratadine, OR: 1.33 (0.73-2.40)

Evidence Table 18. Quality assessment of adverse events in observational studies in adults

Author Year Country	Study design	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Quality score	Funding
CDC 2004	Case control	Yes	Yes	Yes	Yes	Yes	Fair	NR; part of national Birth Defects Prevention Study
Zuberbier 1996 adults and peds	Case series	No	No	Unclear	No	Variable; all participants had 3 days of loratadine; others had up to 21 days	Poor: termed RCT in the abstract but was a case series; no details on AE ascertainment; no detail on AE reporting	NR
Kulthanan 2004	Time series	Yes for somnolence, others no	Yes	No (not blinded)	No	Yes (6 weeks)	Fair	Aventis Pharma Ltd.

Evidence Table 19. Adverse events in adult allergic rhinitis trials with less than 14 days' followup

Author, year country	Method of assessing adverse events	Total withdrawals/ Withdrawals due to adverse events	Adverse events pre-specified and defined?
Day et al., 1997	Recorded by subjects on the backs of symptom score cards.	Total: 19/111 (17.1%) AEs: 5 (intolerable symptoms related to pollen challenge)	No
Day et al., 1998	Incidence and severity of all observed and volunteered adverse experiences were recorded by the investigator. Physical exam and laboratory testing were performed at screening and at the final visit.	Total: 8/202 (4.0%) AEs: 2 (1 cetirizine [asthma symptoms], 1 loratadine [nausea, chest discomfort])	No
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose)	Limited physical exam and laboratory assessments at screening, physical exam repeated at withdrawal or end of study. AEs recorded before entering EEU each day of phases II and II and at the end of the study and whenever AEs were observed and/or reported in the EEU. All subjects contacted by phone at least 1 week after final visit to assess AEs that might have occurred for the week after final dose of medication received.	Total: 12/575 (2.1%) Due to AEs: 0.4% cetirizine, 1.7% fexofenadine	No
Horak et al., 2005	"Safety information was collected by continuously monitoring the AEs and was assessed through the recording of vital signs (blood pressure and heart rate) and FEV1 (in case of occurrence of asthmatic symptoms)."	Total: 10/94 (10.6%) Due to AEs: 2 placebo, 1 levocetirizine (infections)	Not all
Hyo et al., 2005	Not reported	Not reported	No

Evidence Table 19. Adverse events in adult allergic rhinitis trials with less than 14 days' followup

Author, year country	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Funding
Day et al., 1997	Yes	Unclear, reported as double blind	Yes (RCT, similar groups at baseline)	No for most AEs (single dose)	Nordic Merrell Dow, Quebec
Day et al., 1998	Yes	Unclear, reported as double blind	Yes (RCT, similar groups at baseline)	No for most AEs (2 days)	Pfizer
Day et al., 2004 (21 to 24 hours post dose) Day et al., 2005 (5 to 12 hours post dose)	Yes	Unclear, reported as double blind	Yes (RCT, similar groups at baseline)	No for most AEs (2 days)	Pfizer
Horak et al., 2005	Not clear	Unclear, reported as double blind	No	No for most AEs (single dose)	UCB Farchim, Bulle, Switzerland
Hyo et al., 2005	No	Unclear, reported as double blind	Yes (RCT, similar groups at baseline)	No for most AEs (2 days)	NR

Evidence Table 19. Adverse events in adult allergic rhinitis trials with less than 14 days' followup

Author, year country	Method of assessing adverse events	Total withdrawals/ Withdrawals due to adverse events	Adverse events pre-specified and defined?
Lee et al., 2004	Not reported	Not reported	No
Meltzer et al., 1996	Safety assessed by comparing results of physical exams and laboratory evaluations before administration of study medications and within 7 days of completing the study. Investigators assessed the nature, severity, number of all observed or volunteered AEs, and their relation to treatment.	Total: 6/279 (2.2%) Due to AEs: None	No
Passalacqua et al., 2004	Not reported	None	No
Satish et al., 2004	Not reported	Total: 4/48 (8.3%) AEs: Not reported	No
Simons et al. 2000	Patients asked about sleepiness, dry mouth, and other possible adverse events of the medication.	No withdrawals	Yes
Weiler et al., 2000	Not reported	Missing data for 2 of 160 sessions in phase 1 and 6 of 160 sessions in phase 2 (1 participant fell asleep after receiving alcohol and could not be roused, 4 participants had simulator sickness, mechanical failure in 2 instances).	No

Evidence Table 19. Adverse events in adult allergic rhinitis trials with less than 14 days' followup

Author, year country	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Funding
Lee et al., 2004	No	Not reported	No	Unclear (1 week)	University of Dundee departmental grant, no funding from pharmaceutical industry.
Meltzer et al., 1996	Yes		Yes (RCT, similar groups at baseline)	No for most AEs (2 days)	Pfizer
Passalacqua et al., 2004	No	Not reported	No	No for most AEs (single dose)	Associazione Ricerca Malattie Immunologiche e Allergiche.
Satish et al., 2004	No	Not reported	No	No for most AEs (3 doses)	Research support from Integrated Therapeutics Group, Inc.
Simons et al. 2000	Yes	Unclear, reported as double blind	No	No for most AEs (single dose)	NR
Weiler et al., 2000	No	Not reported	No	No for most AEs (single dose)	Grant from Hoescht Marion Roussel, and from NIH.

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse Events (AEs)
Head-to-head trials		
Sienra-Monge 1999	AEs assessed by investigator at final study visit and by parents each day	2 AE reported, both in cetirizine group and necessitating withdrawal from study: 1) somnolence and mild irritability and 2) generalized rash
Active-controlled trials		
Boner 1989	Reported by patients/parents to blinded investigator	*All comparisons are for loratadine 5mg vs dexchlorpheniramine 3 mg* Somnolence on day 1: 0% vs 5.3% Mild epitasis days 1-3: 9.5% vs 0% Moderate epitasis: days 1-2: 4.8% vs 0% Moderate epitasis: days 6-8: 4.8% vs 0% 100% of loratadine patients were sedation-free for the whole trial vs. 79% of dexchlorpheniramine-treated patients One loratadine patients got nausea, vomiting, and lipothymia on 7th day, but investigators felt symptoms not likely related to study drug
Hsieh 2004	Assessed at each visit by adverse event reporting and by the observation of any changes in vital signs. All reported AEs were recorded.	Sedation (5%) reported in cetirizine 20mg group. Sedation and fatigue in montelukast and placebo. NSD among groups.

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Total withdrawals; withdrawals due to AEs	Non-biased selection?	Low overall loss to follow-up?	AEs pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Head-to-head trials								
Sienra-Monge 1999	2 pts; 2 pts (2 pts in cetirizine group,1 with mild irritability and 1 with generalized rash)	Unclear; no data on selection of patients	None; 2 withdrew for AE	Laboratory tests specified; symptoms were not	No, unclear if assessor blinded	Unclear	No, but baseline groups comparable for known confounders	Yes (28d)
Active-controlled trials								
Boner 1989	4; 0	Unclear; no data on selection of patients	10%	No	Yes	Assessor blinded; parent not blinded; unclear if child blinded to treatment	NR; but baseline groups comparable for known confounders	Yes (2 weeks)
Hsieh 2004	5;0	Unclear; no information on patient selection	Yes	No	Yes	Unclear	No	Yes (3 months)

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse Events (AEs)
Jordana 1996	Patients reported AEs in their daily diary	All comparisons are for loratadine 19 mg vs fluticasone 200 micrograms spray: Headache: 25% vs 42% Pharyngitis: 10% vs 16% Severe headaches: 6 pts vs 9 pts (NSD) Event most frequently reported by investigator as 'drug-related' was epitasis; 4% vs 7% Lab values were similar for both drugs at baseline and at end of treatment; abnormal values were considered to be unrelated to treatment
La Rosa 2001	Laboratory testing	Patients on cetirizine did not complain of local or systemic undesirable effects. On Day 7 on the oxatomide group, 1 child had perioral allergic reaction, and child withdrawn. Hematologic, chemical, and urinary tests were within the normal limits for all patients at end of study (NSD between groups)
Lai 2002	Reported by patients; no mention blinding of assessor	No serious adverse events reported AE's given for cetirizine 10mg vs ketotifen 1mg/bid vs oxatomide 1 mg/kg bid vs placebo (NSD for all comparisons) Headache: 0% vs 0% vs 0% vs 6.3% Sedation: 10.5% vs 6.3% vs 11.1% vs 6.3% Nausea: 0% vs 6.3% vs 0% vs 0% Fatigue: 5.3% vs 0% vs 5.6% vs 0%

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Total withdrawals; withdrawals due to AEs	Non-biased selection?	Low overall loss to follow-up?	AEs pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Jordana 1996	12 withdrawals in total (A 7, B 5); 4 withdrawn because of suspected AEs: A 3 (infectious mononucleosis, angioedema, sinus headache) B 1 (asthma exacerbation)	Unclear; no data on selection of patients	Yes, for ITT analysis	No	No	Unclear; blinding of assessor NR	No	Yes (4 weeks)
La Rosa 2001	0; 1	Unclear; no data on selection of patients	5/62	No	No	Unclear; blinding of assessor NR	NR; baseline groups comparable for age, sex, height	Yes (4 weeks)
Lai 2002	4; reasons for withdrawals NR	Unclear; no data on selection of patients	29526	No	No	Unclear; blinding NR	NR, but baseline groups comparable for known confounders	Yes (12 weeks)

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse Events (AEs)
Tinkelman 1996	Tolerability of side effects assessed by investigators as 0 = "requiring discontinuation", 1 = "tolerable", 2 = "not bothersome" 3 = "none"	% of patients reporting AEs: Cetirizine (both dosage groups): 33.6% vs chlorpheniramine: 38.1% Mild to moderate AEs: Certirizine (combined): 98.3% of events (58 of 59 events) vs chlorpheniramine: 91.9% (34 of 37 events) Withdrawals due to AEs: Cetirizine (combined): 0 vs chlorpheniramine: 1 Most commonly reported AEs (no p-values given): Abdominal pain: Cetirizine (combined): 9.6% (12/125 patients) vs chlorpheniramine 4.8% (3/63) Somnolence: Cetirizine qd: 3.6% vs cetirizine bid: 13% vs Chlor 7.9% Fatigue: Cetirizine (combined): 4.0% vs Chlor: 6.3% Nausea and headache: Cetirizine (combined): 3.2% Nausea: Cetirizine (combined): 1.6% Headache: Cetirizine (combined): 6.3%

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Total withdrawals; withdrawals due to AEs	Non-biased selection?	Low overall loss to follow-up?	AEs pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Tinkelman 1996	6, including 2 for an upper respiratory tract infection, 1 for personal reason, 1 for unknown reason	Unclear; no data on selection of patients	6/188	No	Yes	Unclear; blinding NR	Yes, all baseline covariates included in ANOVA	Yes (2 weeks)

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse Events (AEs)
Placebo-controlled trials		
Allegra 1993	AEs obtained from parents in response to a general question and from daily evaluation cards	No severe AEs were reported with cetirizine. Withdrawal occurred in 1 patient on cetirizine 2 patients on placebo because of concurrent asthma and pharyngitis that was considered unrelated to treatment. Mild somnolence, cetirizine 5.5%, placebo 0%
Baelde 1992 Belgium	AEs elicited by questioning pts and parents and from information on symptom report cards	No severe AE were reported; no withdrawals due to AE Tiredness or sleepiness; 3/40 placebo; 4 /43 cetirizine 5mg; 1/42 cetirizine 10mg Leukocytosis: 2/40 placebo; 2/43 cetirizine 5mg, 4/42 cetirizine 10mg; not considered clinically relevant Increase AST levels: 3/43 cetirizine 5mg, 5/42 cetirizine 10mg
Ciprandi 1997a, 1997b	Possible adverse events were recorded in the evening on a diary card; cough was assessed qid by patient report.	No significant adverse events were reported by patients; 1 patient in cetirizine group and 2 in placebo reported an episode of headache
Ciprandi et al, 2001 Italy	NA (AE NR)	None
Jobst et al 1994	From patient daily diaries, interpreted by investigator	Reporting of 1 or more AEs: cetirizine 2.5mg 25%, cetirizine 5mg 14%, cetirizine 10mg 22%, placebo 18% (between-group difference p=0.333); Of 65 patients reporting AEs, 34 patients had mild AE, 37 moderate AEs, 5 severe (cetirizine 2.5mg- 2 severe; cetirizine 5mg- 1severe; cetirizine 10mg- 0 severe; placebo- 2 severe); Most frequent AE among all groups: URI, cough, headache, diarrhea, nausea; no dose-related distributions noted

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Total withdrawals; withdrawals due to AEs	Non-biased selection?	Low overall loss to follow-up?	AEs pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Placebo-controlled tria								
Allegra 1993	3 pts (1 on cetirizine, 2 on placebo); 0	Unclear; no data on selection of patients	Yes (none)	No	AEs reported with daily diaries	Unclear if assessor blinded; open-ended question was asked to patients/parents	NR	Yes (2 weeks)
Baelde 1992 Belgium	4; 0	Unclear; no data on selection of patients	13/138	No	Yes, investigator interview and patient diary	Unclear; blinding of assessor not explicitly reported	NR; multiple pair wise comparisons without adjustment	Yes (2 weeks)
Ciprandi 1997a, 1997b	None	Unclear; no data on selection of patients	0	No	for cough, patient completes questionnaire qid; PEF recorded bid by patient (best of 3)	Unclear; no validation of PEF or cough questionnaire	NR	Yes (4 weeks)
Ciprandi et al, 2001 Italy	0							
Jobst et al 1994	8 in total: cetirizine 2.5: 4 (nausea, bronchitis, fever and vomiting, dizziness and headache); Cetirizine 5 mg: 2 (viral infection, pharyngitis); Cetirizine 10 mg: 1 (tonsillitis, pharyngitis, rash)	Unclear; no data on selection of patients	Yes (17/228)	No	AEs reported with daily diaries	Unclear; investigator recorded AE from patient at each visit	NR	Yes (2 weeks)

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse Events (AEs)
Masi 1993	AEs obtained from patients and parents at end of day on daily diary card; laboratory tests done prior to treatment and at end of study.	AE data given as cetirizine 10mg vs placebo, p not reported AEs reported by 14 pts in cetirizine 10mg and 14 pts in placebo 20 AEs in cetirizine 10mg patients and 19 AEs in placebo patients Somnolence: 9.5% vs 3.3% Headache: 3.2% vs 1.6% Vertigo: 1.6% vs 0% Rash: 3.2% vs 0% Nausea/ vomiting: 0% vs 4.9% Anorexia: 0% vs 1.6% Increased appetite: 1.6% vs 0% Dry mouth: 1.6% vs 0% Abdominal pain: 1.6% vs 1.6% Increased cough: 1.6% vs 4.9% Pharyngitis: 1.6% vs 4.9% Other: 6.3% vs 8.2%
Pearlman 1997	AEs were reported or noted by the investigator were evaluated for time of onset, duration, severity, and relationship to study drug. Patients were instructed to record AE in daily diary. ECG intervals were determined using digitized, validated protocol	Groups cetirizine 5 mg and cetirizine 10 mg are combined as one group as NSD between these groups. Data given as cetirizine groups vs placebo: Majority of AE were mild or moderate (86.5%, 136/157). Most common AE was headache (15.1% vs 19.7%). Other AEs; pharyngitis (10.1% vs 13.6%); abdominal pain (9.4% vs 4.5%); epistaxis (7.1% vs 4.3%). QT interval: NSD between groups and no prolongation in any group at 2-week follow-up; laboratory tests: NSD between groups

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Total withdrawals; withdrawals due to AEs	Non-biased selection?	Low overall loss to follow-up?	AEs pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Masi 1993	10; 3 3 AE withdrawals: 2 on cetirizine (from headache, vertigo, and autonomic symptoms); 1 on placebo for lipothymia	Unclear; no data on selection of patients	Yes; 10/124	No	No	Unclear if assessor blinded; open-ended question was asked to patients/parents	NR	Yes (2 weeks)
Pearlman 1997	16 patients discontinued treatment during trial: intercurrent illness (7), insufficient clinical response (3), poor compliance (2), adverse experience (1), protocol violation (1), baseline ECG abnormality (1), dispensing error (1)	Unclear; no data on selection of patients	16/205 for efficacy; 88 unavailable for 2-w follow-up for ECG analysis	Yes	AEs reported by patients to investigator who appears to be blinded; investigator reviewed patients' daily diary	Unclear; investigator recorded AE from patient at each visit	Yes	Yes (4 weeks)

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse Events (AEs)
Simons 1999, 2001	Symptoms recorded by primary care-giver on a diary card weekly and discussed with investigator. Serious events and AEs potentially attributable to drug were reviewed by a blinded investigator	Serious events reported in cetirizine group (9.3%) and placebo group (11.6%); Serious events attributed to study drug : 1 in cetirizine group and 5 in placebo group. Hospitalizations in cetirizine group (36 children) and placebo (47 (p=0.19) Accidental overdose: 2 children in cetirizine group and 8 in placebo group ast 1 symptom or event reported in the diary card on at least one occasion: 98.5% in cetirizine group and 98.7% in placebo group Most symptoms were mild and were related to URTI, allergic disorders, and not to medications; increased appetite in 2 children in cetirizine group and 1 in placebo group; there were no reports of increased appetite Number of children, cetirizine group vs placebo group Somnolence: 9, 8 (p=0.373) Insomnia: 35, 21 (p=0.071) Mean increases in height and weight were appropriate Behavioral Screening Questionnaire: NSD between groups ECG: NSD QT interval between groups (p NR) Hematology and biochemical tests: NSD between groups
Wahn 2003, Meltzer 2004	NR	Overall AEs: fexofenadine: 18.3%, placebo 18.7 (NSD); treatment-emergent AEs (>1%): headache, epistaxis, URI, pharyngitis, sinusitis, nausea, rash); NSD between groups for any of these events
Yang et al 2001	NR	No adverse event was recorded

Evidence Table 20. Adverse events in efficacy trials in children

Author Year Country	Total withdrawals; withdrawals due to AEs	Non-biased selection?	Low overall loss to follow-up?	AEs pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Simons 1999, 2001	Cetirizine 48 and placebo 51; 11 and 15 due to symptoms or events; unclear how many of these were due to AE potentially related to study drug	Unclear, no information on selection	12%; NSD between groups	No	Yes; blinded observer for serious AEs	Yes for serious AEs	NR	Yes (18m)
Wahn 2003, Meltzer 2004	3 children in fexofenadine-treated group withdrew from study, but not considered to be related to treatment (asthma,	Unclear; no data on selection of patients	3/935	No	No	Unclear; blinding of assessor not explicitly reported	NR	Yes (2 weeks)
Yang et al 2001	None	Unclear; no data on selection of patients	14/60	No	No	Unclear; investigator recorded AE from patient at each visit	NR	Y (3 weeks)

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Placebo-controlled trials			
Cetirizine			
Simons 2003 US and Canada (Fair)	Randomized, double-blind, Multicenter, parallel group	85 infants 6 - 11 months, inclusive; outpatients with a history of H1-antihistamine treatment for allergic rhinitis, urticaria, atopic dermatitis, or other disorders.	Body weight or length below the fifth percentile; history of sleep apnea or a sibling with sleep apnea or sudden infant death syndrome; and allergy or intolerance to cetirizine, any of its constituents, or other piperazine H1-antihistamines. Infants were excluded if they had a QTc interval of greater than 450 ms or if their parent/caregivers were unlikely to record observations reliably or had evidence of alcohol or drug dependence.

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Age Gender Race/ethnicity	Interventions	Allowed other medications/ interventions
Placebo-controlled trials			
Cetirizine			
Simons 2003 US and Canada (Fair)	Mean age 8 months (range 6 to 11 months) 48% male Ethnicity NR	C: Cetirizine 0.25 mg/kg P: placebo bid 7 days.	Infants were excluded if they needed to use one or more of the following medications within the time period specified before enrollment: H-1 antihistamines or cough/cold preparations within 7 days, systemic corticosteroids within 28 days, and systemic antibiotics within 7 days.

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Method of AE assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Placebo-controlled trials			
Cetirizine			
Simons 2003 US and Canada (Fair)	Before randomization, a complete medical history was obtained from the parent/caregiver, and baseline symptoms relating to sleep patterns, irritability, and tremor were recorded. A physical examination was performed, and vital signs were recorded. Baseline QT interval was measured ona 12-lead ECG and corrected for heart rate. Diary: Parents/caregivers answered yes or no to questions about changes in sleep pattern, nervousness, irritability, or tremor during the previous 24 hours. At the second and last visit, conducted 7 days after the initial visit or at early withdrawal, another complete physical examination,including vital sign, and a 12-lead ECG was obtained approximately 2 hours after the last dose of the study drug. Review of information in the diary and interview were also used to determine the incidence of adverse events. A followup telephone interview was conducted 7 days after the second visit to assess subsequent adverse events.	90/90/85	9/0/85

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Adverse Events
Placebo-controlled trials	
Cetirizine	
Simons 2003 US and Canada (Fair)	*C vs P* All-cause adverse events: 73.8% vs 88.4% Treatment-related adverse events: 45.2% vs 62.8% All-cause adverse events (*cetirizine vs placebo*) Nervousness: 28.6% vs 44.2% Insomnia: 23.8% vs 44.2% Somnolence: 21.4% vs 30.2% Toothache: 9.5% vs 9.3% Diarrhea: 7.1% vs 9.3% Otitis media: 7.1% vs 4.7% Upper respiratory tract infection: 7.1% vs 2.3% Agitation: 4.8% vs 16.3% Tremor: 4.8% vs 4.7% Fever: 4.8% vs 4.7% Cough: 0% vs 4.7% Pharyngitis: 4.8% vs 0% Rash: 2.4% vs 4.7% Rhinitis: 4.8% vs 4.7% Responses in daily diary entries by parents/guardians (*cetirizine vs placebo*) Abnormal increase in sleep: 29.3% vs 30.2% Abnormal decrease in sleep: 24.4% vs 37.2% Abnormal restlessness during sleep: 39.0% vs 51.2% Abnormal irritability/fussiness: 46.3% vs 46.5% Tremor: 4.9% vs 4.7% No significant prolongation of the QT interval by cetirizine was found (p=0.98; 95% CI for mean difference between groups, -4.74 to 4.60).

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Total withdrawals; withdrawals due to adverse events
Placebo-controlled trials	
Cetirizine	
Simons 2003 US and Canada (Fair)	Total withdrawals: 9 ; 6 due to AEs *Cetirizine vs placebo:* Total withdrawals: 11.9% vs 9.3% Withdrawals due to AEs: 2.4% vs 4.7%

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Winder 1996 (Fair)	randomized PCT, parallel Multicenter	Children in good health between 6 and 11y with a documented history of SAR during the fall pollen season and allergen sensitivity confirmed by a radioallergosorbent test or an intradermal or skin prick test within the past 2 years. At entry, pts had to be symptomatic for SAR as determined by a minimum symptom score.	Pts excluded if they had any clinically significant concomitant disease(s) or any medical condition that could interfere with evaluation of response. Pts who had a medical history of severe asthma attacks during the pollen season were also excluded. Pts receiving an escalating course of desensitization or who had been on a maintenance regimen for <6 months were excluded. Pts with a history of allergic reaction to hydroxyzine or cetirizine, and pts who had participated in a cetirizine trial or received an investigational drug within 1 month before study were excluded.
Placebo-controlled trials			
Desloratadine			
Bloom 2004 USA **2-5y arm** (Fair)	Placebo-controlled, parallel single center	Children 2-5 y with a documented history of AR or CIU. Pts with AR had either a positive radioallergosorbent test (RAST) or a positive skin test response to an appropriate allergen. Subjects were required to be in general good health, confirmed by physical examination and routine clinical and laboratory testing, and free of clinical significant disease that would interfere with study evaluations.	Pts were excluded if they had a history of allergies to >2 classes of medications, were allergic to or could not tolerate antihistamines, or had a history of hyper sensitivity to the study drug or its excipients. Pts excluded if they had had an upper respiratory tract or sinus infection that required antibiotic therapy within 14d before the screening visit, a viral upper respiratory infection within 7d before the screening visit, or if they had a history of noncompliance with medications or treatment protocols, or with conditions that would interfere with the ability of the parent or guardian to reliably complete a drug diary. Medications prohibited byefore study enrollment and during the study included corticosteroids; nasal cromolyn sodium or nedocromil; systemic antihistamines; topical nasal, oral, or ocular decongestants; systemic antibiotics; and immunotherapy (unless a stable maintenance dose was prescribed). Appropriate washout was necessary before study entry.

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Age Gender Race/ethnicity	Interventions	Allowed other medications/ interventions
Winder 1996 (Fair)	Mean age: 8.85y Range: 6-11 y 66.7% male 88.4% white 10.6% other	C1: cetirizine 5 mg C2: cetirizine 10 mg P: placebo 4-week treatment	Pts required to discontinue nasal decongestants for 24j, antihistamines for 48h, and cromolyn sodium or inhaled, intranasal, or topical steroids for 2 weeks before and during the study.. The use of oral steroids or astemizole within 2 months of study was not permitted.
Placebo-controlled trials			
Desloratadine			
Bloom 2004 USA **2-5y arm** (Fair)	Mean: 3.45y 55.8% male White: 23.4% African American: 75.7% Other: 1.0%	<u>15-day treatment</u> D: Desloratadine syrup 1.25 mg (2.5 mL) P: Placebo	only certain medications allowed; see "Exclusion criteria" for list of medications not allowed

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Method of AE assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Winder 1996 (Fair)	ECGs obtained at baseline and day 14 (+/- 3) though many ECGs obtained after day 14 so they are referred to as "end-point ECGs"; physical exams and lab tests performed at baseline and final visit (week 4). pts completed a diary with the help of a parent/guardian at the end of each week, which had space for AEs; and investigators interviewed each pt about AEs at the end of each study week.	NR/ NR/ 209	16 /NR / 209 for safety; 202 for ECGs
Placebo-controlled trials			
Desloratadine			
Bloom 2004 USA **2-5y arm** (Fair)	From daily diaries recorded by parents/guardians , interpreted by investigator, and interviews conducted with subject and/or parent	NR/ NR/ 111	0 / 0 /111

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Adverse Events
Winder 1996 (Fair)	No clinically significant abnormal ECGs leading a change in treatment; no arrhythmia observed. Adjusted mean change in QTc between baseline and endpoint analysis, C1 vs C2 vs P: -5.09 (p<0.05 C1 vs C2 and P); + 6.79 (NSD), +2.44 (NSD) Total AEs: 157 events across groups *Data given as all cetirizine pts vs placebo* Headache: 15% vs 18.8% Pharyngitis: 10.0% vs 13.0% Abdominal pain: 9.3% vs 4.3% Epistaxis: 7.1% vs 4.3% No pronounced differences between AEs experienced between C1 and C2 No clinically significant effects on lab evaluations related to study medication
Placebo-controlled trials	
Desloratadine	
Bloom 2004 USA **2-5y arm** (Fair)	*Results given as D vs P (no appreciable differences noted between groups per investigators)* Any adverse event: 12.7% vs 10.7% with no serious AEs or death Fever: 5.5 vs 5.4% Headache: 1.8 vs 5.4% Viral infection: 1.8 vs 1.8% Otitis media: 0 vs 1.8% Varicella: 3.6% vs 0% Rash: 1.8% vs 0% Urinary tract infection: 3.6% vs 0% Gastroenteritis: 0 vs 0% Vomiting: 0 vs 0% No clinically relevant changes noted in median clinical lab test values or mean vital signs

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Total withdrawals; withdrawals due to adverse events
Winder 1996 (Fair)	16; 1 (6 pts from C1, 4 pts from C2, and 6 pts from P)

Placebo-controlled trials	
Desloratadine	
Bloom 2004 USA **2-5y arm** (Fair)	NR; NR

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Bloom 2004 USA **6-11y arm**	Placebo-controlled, parallel single center	Children 6-11y with a documented history of AR or CIU. Pts with AR had either a positive radioallergosorbent test (RAST) or a positive skin test response to an appropriate allergen. Subjects were required to be in general good health, confirmed by physical examination and routine clinical and laboratory testing, and free of clinical significant disease that would interfere with study evaluations.	Pts were excluded if they had a history of allergies to >2 classes of medications, were allergic to or could not tolerate antihistamines, or had a history of hyper sensitivity to the study drug or its excipients. Pts excluded if they had had an upper respiratory tract or sinus infection that required antibiotic therapy within 14d before the screening visit, a viral upper respiratory infection within 7d before the screening visit, or if they had a history of noncompliance with medications or treatment protocols, or with conditions that would interfere with the ability of the parent or guardian to reliably complete a drug diary. Medications prohibited byefore study enrollment and during the study included corticosteroids; nasal cromolyn sodium or nedocromil; systemic antihistamines; topical nasal, oral, or ocular decongestants; systemic antibiotics; and immunotherapy (unless a stable maintenance dose was prescribed). Appropriate washout was necessary before study entry.
Placebo-controlled trials			
Loratadine			
Grimfeld et al 2004 International (51 centers) Preventia I Study (Fair)	PCT Phase 1: DB, randomized, Multicenter, parallel Phase II: 12 month follow-up without medication	Children in good health between 12-24 months at enrolment and have had ≤ 2 episodes of wheezing and have experienced ≥ 5 episodes of rhinitis, rhinopharyngitis, acute otitis media, laryngitis, or bronchitis during the previous 12 months.; they had to be free of any clinically significant disease other than atopy or respiratory infections that could interfere with the study. A child's parent/guardian had to be willing and able to comply with the requirements of the study.	exclusion criteria as follows: child suffering from any chronic pulmonary disease, allergy to loratadine syrup or any other drug, medical illness (renal, heaptic, cardiovascular and nuerologic), abnormal vital sign, abnormal weight or height not because of a known underlysing disease or clinically significant malnutrition, clinical significant abnormal lab values (except if because of a known underlying disease), personal or familial (parent or sibling) history of sleep apnea, participation in a drug trial within 30 days prior to study entrance, desensitization or immunotherapy with allergen extracts undergone prior to enrolment, immunosuppressive treatment or readiation therapy over the past 6 months (or expected to be required during the study). Previous drug administration required a washout period prior to enrolment: systemic corticosteroids (30 days), inhaled or nasal corticosteroids (14 days), cromolyn sodium (14 days), antihistamines (7 days) and immunostimulators (30 days).

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Age Gender Race/ethnicity	Interventions	Allowed other medications/ interventions
Bloom 2004 USA **6-11y arm**	Mean: 8.2y 43.3% male White: 41.7% African American: 56.7% Other: 1.7%	15-day treatment D: desloratadine 2.5 mg (5 mL) P: placebo	only certain medications allowed; see "Exclusion criteria" for list of medications not allowed
Placebo-controlled trials			
Loratadine			
Grimfeld et al 2004 International (51 centers) Preventia I Study (Fair)	Mean age: 23.95 months Range: 60.7% male White: 73.2% Black: 0.7% Hispanic: 18.2% Asian: 6.6% Other: 0.5%	L (n=204): Loratadine 2.5 mg qd if under 24 months, if over 24 months, Loratadine 5 mg qd P (n=208): placebo	Unclear

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Method of AE assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bloom 2004 USA **6-11y arm**	From daily diaries recorded by parents/guardians , interpreted by investigator, and interviews conducted with subject and/or parent	NR/ NR/ 120	0/ 0/ 120
Placebo-controlled trials			
Loratadine			
Grimfeld et al 2004 International (51 centers) Preventia I Study (Fair)	Vital signs and psychomotor development evaluated at each visit. Changes in physical exams were evaluated at visits 1, 6, (end of treatment phase) and 10 (end of follow-up phase). Lab values and EKG were recorded at visit 1 and at the end of the 12-month treatment phase. AEs reported by parents and physicians	NR/ NR/ 412	71 / 22/ for 12 month treatment phase: 412; for 24 month study period: 327

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Adverse Events
Bloom 2004 USA **6-11y arm**	*Results given as D vs P* Any adverse event: 1.7% vs 10% Fever: 0% vs 0% Headache: 1.7% vs 6.7% Viral infection: 0 vs 0% Otitis media: 0 vs 0% Varicella: 0 vs 0% Rash: 0 vs 0% Urinary tract infection: 0 vs 0% Gastroenteritis: 0 vs 3.3% Vomiting: 0 vs 3.3% No clinically relevant changes noted in median clinical lab test values or mean vital signs
Placebo-controlled trials	
Loratadine	
Grimfeld et al 2004 International (51 centers) Preventia I Study (Fair)	*All AEs given as L vs P* Total number of respiratory infections per patient/month during 12month treatment phase for all children: 6.2 vs 6.2, p=0.60; for allergic children: 6.0 vs 6.3, p=0.79 Total # of respiratory infections per pt/month during 24 month study period: for all children: 11.6 vs 11.3, NSD; for allergic children: 3.7 vs 4.8, p=0.20 Mean # of repiratory exacerbations/patient during 12-month and 24-month periods: 0.8 vs 1.1, p=0.02 and 1.8 vs 1.9, p =0.5984 All AEs were not significantly different between groups: insomnia: 0 vs 1.0%; irritability: 0 vs 0.5%; somnolence: 0.5 vs 1.0%; pharyngitis: 18.8 vs 18.1%; bronchitis: 15.8 vs 13.0%; otitis media: 9.1 vs 13.0%; gastroenteritis: 7.9 vs 7.9%; rhinitis: 7.9 vs 7.3%; fever: 6.7 vs 7.3%; varicella: 8.5 vs 4.5%; coughing: 7.3 vs 5.1%; tonsillitis: 5.5 vs 5.1%; viral infection: 5.5 vs 4.5%; vomiting: 5.5 vs 3.4% EKG changed in 4 pts from each group from baseline: in L, changes were (n=1 for each): disturbances in ventricular repolarization, lengthening of QT interval, sinus bradycardia, sinus arrhythmia; in placebo (n=1 for each): lengthening of PR interval, right ventricular hypertrophy, lengthening of QT interval, left overloa

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Total withdrawals; withdrawals due to adverse events
Bloom 2004 USA **6-11y arm**	NR; NR
Placebo-controlled trials	
Loratadine	
Grimfeld et al 2004 International (51 centers) Preventia I Study (Fair)	71 withdrawn from treatment phase; 102 total withdrew from both phases. Withdrawals due to AEs: 1 from placebo

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Placebo-controlled trials			
Fexofenadine			
Graft 2001 **Meltzer** 2004 (Fair)	Randomized, double-blind, parallel group, Multicenter	SAR Children ages 6 to 11 years, with a history of SAR and (+) skin test response to at least one fall allergen indigenous to the study site area. Inclusion was also based on symptom severity. A TSS of ≥6, and ≥2 symptoms (excluding nasal congestion) with a minimum score of 2, were required for enrollment (maximum score 16).	Significant symptom reduction during placebo lead-in; URI, sinusitis, or otitis media within 30d of study entry, immunotherapy to treat SAR; and clinically significant cardiovascular, hepatic, neurologic, psychiatric, endocrine, or other major systemic disease;

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Age Gender Race/ethnicity	Interventions	Allowed other medications/ interventions
Placebo-controlled trials			
Fexofenadine			
Graft 2001 **Meltzer** 2004 (Fair)	mean age: 9.1y, range 5-12 % male: 59 86% Caucasian 9% Black Weight: 36 kg (11), range 18-93	F1: fexofenadine 15mg bid F2: fexofenadine 30 mg bid F3: fexofenadine 60mg bid P: placebo	NR

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Method of AE assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Placebo-controlled trials			
Fexofenadine			
Graft 2001 **Meltzer** 2004 (Fair)	AEs reported by caregiver in daily dairy; 12-lead ECG	1594/NR/NR	NR/NR/875

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Adverse Events
Placebo-controlled trials	
Fexofenadine	
Graft 2001 **Meltzer** 2004 (Fair)	Most common AE: headache: group F1 8.0%, F2 7.2%, F3 9.4% P 6.6%; headache was only AE felt to be possibly related to treatment, occurred in 1-2% in all groups; somnolence reported by 2 patients in P and 1 in F1 ; other reported AEs (>2% in the active treatment groups: URI, pharyngitis, coughing, injury/accident/ abdominal pain, fever, headache (NSD among groups); NSD among groups for corrected QT interval; NSD in chemical and blood cell testing; correlation ($p<0.05$) was noted between each of white blood count, total lymphocyte count. chloride, and magnesium and higher drug dosage; one serious AE: status asthmaticus (considered unlikely related to study drug)

Evidence Table 21. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality Score)	Total withdrawals; withdrawals due to adverse events
Placebo-controlled trials	
Fexofenadine	
Graft 2001 **Meltzer** 2004 (Fair)	38 patients discontinued trial early:, 10 due to AEs, 5 in treatment groups and 5 in placebo; AEs in treatment group included URI, otitis media, asthma; no AE that results in discontinuation was attributed to study medication

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Head-to-head trials						
Delgado 1998 Brazil	Method NR	NR	Cetirizine group significantly older than terfenadine and astemizole groups.	yes	NR	NR
Placebo-controlled trials						
Bloom 2004 USA **6-11y arm**	Method NR	NR	Yes	Yes	States "double blind" but no details	States "double blind" but no details
Bloom 2004 USA **2-5y arm**	Method NR	NR	Yes	Yes	States "double blind" but no details	States "double blind" but no details
Graft 2001	Method NR	Not reported	No: fexofenadine 30 mg and 60 mg hlower+D4 weight; no other differences noted; baseline characteristics reported for 872 of 875 randomized	Yes	States "double blind" but no details	States "double blind" but no details

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding
Head-to-head trials						
Delgado 1998 Brazil	NR	NR	NR	unclear- no mention of withdrawals	none reported	Conselho Nacional de Pesquisa Brazil.
Placebo-controlled tria						
Bloom 2004 USA **6-11y arm**	Yes	states "no major deviations from subject compliance" appears to be no attrition	no	Yes	No	Schering-Plough
Bloom 2004 USA **2-5y arm**	Yes	states "no major deviations from subject compliance" appears to be no attrition	no	Yes	No	Schering-Plough
Graft 2001	Yes	Attrition yes, others no	No	No; 38/875 were not evaluated for safety	No	Aventis Pharmaceuticals

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Adequate duration of follow-up?	Quality score	Number screened /eligible/ enrolled
Head-to-head trials						
Delgado 1998 Brazil	Yes	Not clear: "ECG was performed using standard techniques"	Unable to determine.	Yes (14 days)	Poor	NR/NR/80
Placebo-controlled tria						
Bloom 2004 USA **6-11y arm**	Yes	Yes	not clear if blinded.	15 days	Fair	NR/NR/231
Bloom 2004 USA **2-5y arm**	Yes	Yes	not clear if blinded.	15 days	Fair	NR/NR/231
Graft 2001	Yes	Yes	Unclear if blinded	Yes (2 weeks)	Fair	1594/875/875

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care
Head-to-head trials			
Delgado 1998 Brazil	None; 1-week wash-out of H1-receptor antagonists and 4-week wash-out of 2nd generation antihistamines	No	All children received antihistamines; details of concurrent care NR for any group
Placebo-controlled tria			
Bloom 2004 USA **6-11y arm**	No	NR	yes
Bloom 2004 USA **2-5y arm**	No	NR	yes
Graft 2001	1w placebo lead-in	NR	

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Salmun 2000 USA	Method NR	NR	Yes, but not clear if characteristics are reported for randomized or analyzed	Yes	States "double blind" but no details	States "double blind" but no details
Simons 2003 US and Canada	Method NR	NR	Yes	yes	States "double blind" but no details	States "double blind" but no details
Winder 1996	Method NR	NR	Differences in systolic blood pressure (102.6 vs 102.0 vs 99.7 for placebo vs cetirizine 5 mg vs cetirizine 10 mg, p=0.012)	yes	States "double blind" but no details	States "double blind" but no details

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding
Salmun 2000 USA	Yes	No	Unclear	Unable to determine	NR	Schering-Plough
Simons 2003 US and Canada	yes	Attrition yes, others no (89.4% completed)	No	Not clear for ECG, yes for other adverse events.	No	Pfizer
Winder 1996	yes	attrition yes	NR	No- analyzed 196/209 patients with an ECG within 2 days of the last dose, and 121 with a final ECG taken at the second weekly visit (14 +/- 3 days).	No	Pfizer

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Adequate duration of follow-up?	Quality score	Number screened /eligible/ enrolled
Salmun 2000 USA	Yes	Yes	Not clear.	yes	Poor- unable to determine number enrolled, analyzed, withdrawn, because of ambiguous language, "121 children were enrolled and completed the multiple-dose tolerability study."	NR/NR/121?
Simons 2003 US and Canada	Yes	Yes	Yes	? (7 days)	Fair	90/NR/85
Winder 1996	Yes- ECG	Yes	Yes	yes	Fair	NR/NR/209

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care
Salmun 2000 USA	no run-in, washout depending on drug	no	NR
Simons 2003 US and Canada	no	No	NR
Winder 1996	24-hour to 2-week washout, depending on medications	No	yes

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Observational studies						
Rossi 2004 Time series	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)
Zuberbier 1996 adults and peds Case series	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding
Observational studies						
Rossi 2004 Time series	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	NR
Zuberbier 1996 adults and peds Case series	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	Not applicable (NA)	NR

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Adequate duration of follow-up?	Quality score	Number screened /eligible/ enrolled
Observational studies						
Rossi 2004 Time series	No	No	Unclear	yes (4 weeks)	Poor: no details on AE ascertainment or reporting	NA
Zuberbier 1996 adults and peds Case series	No	No	Unclear	Variable; all participants had 3 days of loratadine; others had up to 21 days	Poor: termed RCT in the abstract but was a case series; no details on AE ascertainment or reporting	NA

Evidence Table 22. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care
Observational studies			
Rossi 2004 Time series	NA	NA	NA
Zuberbier 1996 adults and peds Case series	NA	NA	NA

Evidence Table 23. Placebo-controlled trial in children with atopic dermatitis (ETAC)

Author Year Country (Quality Rating)	Study Design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ethnicity
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 1999 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada (Fair)	Double-blind, placebo-controlled, parallel group, multicenter	Infants 1 to 2 years, with active symptoms of atopic dermatitis for at least 1 month before inclusion and at least one parent or sibling with a history of atopic dermatitis, allergic rhinitis, or asthma.	Infants with asthma, or with a history (beyond the age of 6 months) of one or more episodes of wheezing or nocturnal cough as well as any conditions that might obscure the diagnosis of asthma. Weight below the third percentile, chronic pulmonary disease, severe neurologic or psychologic disorder, any third disease likely to interfere with the study drug, clinically relevant cardiac disease, any anomaly of the QT interval on ECG tracing, a history of sleep apnea in the subject or siblings, neonatal distress, prior desensitization or immunotherapy, prior treatment with medicines interfering with the immune system, hypersensitivity to cetirizine or other piperazines or parabens, and participation in a clinical study within 3 months before randomization.	17.0 months (SD4.1) 62.1% male Race/ethnicity NR

Evidence Table 23. Placebo-controlled trial in children with atopic dermatitis (ETAC)

Author Year Country (Quality Rating)	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 1999 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada (Fair)	C: cetirizine oral solution 0.50 mg (0.25 mg twice daily) N: placebo twice daily 18 months	All concomitant medications were allowed but had to be recorded by the parents/guardians on the diary card and by the investigator in the case report form. Investigators were discouraged from using antihistamines except when considered absolutely necessary	(Primary outcome was reduction in incidence of asthma.) Secondary efficacy outcomes included any reduction in severity of symptoms related to atopic dermatitis. Severity of atopic dermatitis rated with SCORAD rating scale. Assessments at baseline, 1 month, 3 months, and thereafter every 13 weeks during the 18-month treatment period. Between visits, parents/guardians were contacted additionally be telephone. At each visit, infants underwent a physical exam where the status of atopy, the severity of AD according to SCORAD, the consumption of concomitant topical and systemic medications, and the occurrence of any concurrent illness were recorded.	830/NR/NR

Evidence Table 23. Placebo-controlled trial in children with atopic dermatitis (ETAC)

Author Year Country (Quality Rating)	Number withdrawn/ lost to fu/ analyzed	Efficacy Results
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 1999 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada (Fair)	99/NR/795	Severity of atopic dermatitis decreased in both groups over 18 months; but NSD between cetirizine and placebo. Change from baseline to 18 months in SCORAD Cetirizine: -9.7 Placebo: -9.4 (NSD) Concomitant use of oral H1-antihistamines: Cetirizine: 18.6% Placebo: 24.9% (p=0.03) In subset of patients with more severe SCORAD at baseline (≥ 25 points; 43.7% of patients): Severity decreased significantly in both groups, but no treatment effects. Concomitant use of corticosteroids: Cetirizine: 25.8% of days (median 6.2) Placebo: 35.1% of days (median 20.2) (p=0.014)

Evidence Table 23. Placebo-controlled trial in children with atopic dermatitis (ETAC)

Author Year Country (Quality Rating)	Safety Results
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 1999 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada (Fair)	Serious adverse events (C vs P) 37/399 children (9.3%) vs 54/396 children (13.6%) p=0.053 Serious adverse events attributed to study medicaiton 1 child vs 5 children Neurological symptoms or events (C vs P) Ataxia (loss of balance): 2 vs 2 (p=1.00) Febrile convulsions: 2 vs 4 (p=0.45) Fatigue: 13 vs 15 (p=0.093) Emotional lability: 5 vs 6 (p=0.772) Hyperkinesia: 5 vs 9 (p=0.296) Insomnia: 35 vs 21 (p=0.071) Nervousness: 5 vs 7 (p=0.577) Other: 5 vs 6 (p=0.772) Somnolence: 9 vs 8 (p=1.00) Total: 65 vs 55 (p=0.373) Hospitalizations: 36 C, 47 P (p=0.189) Most common reasons for hospitalization were infection-related events without asthma (12 C vs 18 P) or injury, surgery, or procedure (8 C vs 15 P) 2 C and 8 P had accidental overdose. Height and weight: Children in both groups had age-appropriate gains in height and weight over 18 months. Cetirizine-treated children weighed significantly less than placebo-treated children at baseline. At other time points, differences were not significant. Mean weight after 18 months: C: 14.82 kg (SD 1.89) P: 14.57 kg (SD 1.87) ECG (missing baseline data on 13 cetirizine-treated and 9 placebo-treated children; missing followup data on 49 cetirizine-treated and 54 placebo-treated children): All within normal limits at baseline and 2 followup visits; no difference between groups in mean corrected QT interval; no child receiving cetirizine had an increase in QT interval.

Evidence Table 23. Placebo-controlled trial in children with atopic dermatitis (ETAC)

Author Year Country (Quality Rating)	Adverse events: behavioral, cognitive, psychomotor development
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 1999 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada (Fair)	Behavior problems (measured by BSQ behavioral screening questionnaire): No effect of cetirizine on children's behavior or a rebound effect after terminating the treatment period. Overall estimated treatment effect as (difference in overall means for cetirizine and placebo): 0.12 (95% CI -0.34, 0.58). Cognitive ability (measured by GCI, a composite scale of the MSCA, measuring verbal, perceptual performance, quantitative memory, and motor aspects, scaled according to age, normal range is 84-116): Overall estimated treatment effect (overall difference in cetirizine and placebo means): -0.81 (95% CI -4.06, 2.43). Developmental milestones (gross motor, fine motor, and speech/language development): No significant differences between groups.

Evidence Table 24. Quality assessment of placebo controlled trial in children with atopic dermatitis (ETAC)

Internal Validity

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 2002 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada	Yes	Yes	Yes, Similar; Diepgen Table pg 280	Yes	Yes	Yes	Yes

Evidence Table 24. Quality assessment of placebo controlled trial in children with atopic dermatitis (ETAC)

Author Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Funding	Quality Rating
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 2002 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada	Attrition and adherence yes; contamination and crossovers: reports children taking oral antihistamines and other concomitant medication during 18-month followup as an outcome measure.	No, total attrition 99/795=12.5%	Unable to determine	Unable to determine	UCB, S.A. (Brussels, Belgium).	Fair

Evidence Table 24. Quality assessment of placebo controlled trial in children with atopic dermatitis (ETAC)

External Validity

Author Year Country	Number screened/ eligible/ enrolled	Run-in/ Washout	Class naïve patients only	Control group standard of care
ETAC (Early Treatment of the Atopic Child) Trial Diepgen et al. 2002 (efficacy); Simons et al., 2002 (safety); Stevenson et al., 2002 (adverse events: behavioral, cognitive, psychomotor development) Multiple European countries and Canada	830/NR/NR	Patients taking systemic corticosteroids, cromoglycate or oral antihistamines for any reason at screening were requested to stop medications and return for baseline evaluation after a washout period (length of period not specified).	NR	Yes

Evidence Table 25. Trials in adults that examined subgroups

Author, Year, Subgroup	Agents	Trial Characteristics
Aaronson et al., 1996 PAR and Asthma	Cetirizine 20 mg qd; albuterol prn; pseudoephedrine rescue.	PAR and asthma, 28 patients, 26 weeks. ITT efficacy. Inclusion: ages 12-65 + skin test; FEV1 ≥ 50%, prednisone, improved 15% by albuterol w/o seasonal exacerbations. Exclusions: pregnant/lactating/no contraception, i/a diagnosis or meds, ADEs AH. Baseline similar: All Caucasian, 54% male, 29.7 years
Diav-Citrin et al., 2003 Pregnancy	Prospective controlled cohort on exposure of pregnant women to antihistamines	Israeli teratogen counseling service followed 210 pregnancies exposed to loratadine (77.9% in 1st trimester) and 267 to other antihistamines (64.6% in the first trimester) to 929 controls.
Einarson et al., 1997 Pregnancy	Prospective controlled cohort on exposure of pregnant women to hydroxyzine or cetirizine	Canadian counseling service for safe exposure to drugs followed all patients requesting information on HTD or cetirizine use during pregnancy 1989-1994 for major malformation and pregnancy outcomes.
Grant et al., 1995 SAR and Asthma	Cetirizine 10 mg qd; albuterol prn, pseudoephedrine rescue, theophylline if stable	SAR and asthma, US, Fall, multicenter, randomized, double-blind, placebo-controlled, 6 weeks. Inclusion/exclusion: ages 12-70, SAR, FEV1 50-80%, prednisone and 15% + with bronchodilator, + skin test within 2 years. No severe AR or asthma, i/a dx, ADEs, previous cetirizine investigation or investigational drug in past 1 month. Baseline similar: age 28, 56% female, 82% Caucasian, diagnosis 18 years, 23-30% on theophylline, 57-65% FEV1 50-84%, ITT safety ? efficacy
Moretti et al., 2003 Pregnancy	Prospective controlled cohort on exposure of pregnant women to loratadine	Teratology information service (Canada, Israel, Italy and Brazil) followed up on contacts for loratadine exposure in 161 patients during first trimester,
Seto et al., 1997 Pregnancy	Meta-analysis of 1st trimester pregnancy antihistamine exposure 1960-1991.	24 studies met criteria (85 rejected for animal studies, case reports, reviews, duplicates or irrelevant) with over 200,000 women.
Wilton et al., 1998 Pregnancy	Observational cohort on exposure of pregnant women in 1st trimester to newly marketed agents.	UK prescription event monitoring reported 831 of 2511 pregnancies in 2467 women exposed to newly marketed drug (included 20 cetirizine pregnancies and 18 loratadine) in 1st trimester, 74 in 2nd and 3rd trimesters.

Evidence Table 25. Trials in adults that examined subgroups

Author, Year, Subgroup	Results	Quality
Aaronson et al., 1996 PAR and Asthma	Efficacy: Significantly improved asthma score, not albuterol use or PFTs Total AE d/c: 10.28 (35.7%) cetirizine 4 (28.5%) placebo 6 (42.8%) d/c from AE: 0	Fair
Diav-Citrin et al., 2003 Pregnancy	NS difference between groups major anomalies loratadine vs. control RR 0.77 (95% CI 0.27 to 2.19) and loratadine vs. other antihistamines RR 0.56 (95% CI 0.18 to 1.77)	Fair
Einarson et al., 1997 Pregnancy	Of 120 pregnancies, 81 hydroxyzine, 39 cetirizine, 75% in first trimester (hydroxyzine 65%, cetirizine 95%). NS difference between exposed groups or control.	Fair
Grant et al., 1995 SAR and Asthma	Efficacy: Cetirizine significant vs. placebo SAR, asthma no worse in season, better asthma score, NS PFTs. Total AE over 4% patients: Cetirizine 43 pts (46%) placebo 45 pts (48%) d/c: cetirizine 9/93 (9.6%), placebo 24/93 (25.8%) d/c from AE: cetirizine 0, placebo 1 joint stiffness, nervousness	Fair
Moretti et al., 2003 Pregnancy	NS difference RR 0.88 (95% CI 0.27 to 2.82).	Fair
Seto et al., 1997 Pregnancy	Found NS difference in trials of women using antihistamines for nausea and vomiting. OR 0.76 (95% CI:0.60-0.94).	Fair
Wilton et al., 1998 Pregnancy	Follow-up of 780 (94%) of pregnancies showed NS difference with controls.	Fair