Drug Class Review

Newer Antihistamines

Final Report
Update 2
Evidence Tables

May 2010

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The literature on this topic is scanned periodically.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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Abbreviations used in Evidence Tables

Abbreviation	Term
A, AST	Astemizole 10mg
A1	Azelastine nasal
A2	Azelastine nasal + loratadine
ACT	Active control trial
AD	Atopic dermatpitis
AE	Adverse event
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
AR	Allergic rhinitis
BID	Dosing twice daily
BSQ	Behavioral screening questionnaire
C	Cetirizine
CGI	Global clinical impression
CIU	Chronic idiopathic urticaria
CNS	Central nervous system
DB	Double-blind
D/C	Discontinued
DLQI	Dermatology Life Quality Index
ECG, EKG	Electrocardiogram
EEU	Environmental exposure unit
ETAC	Early Treatment of the Atopic Child
F/U	Follow-up
FEV1	Forced expiratory volume in 1 second
GI	Gastrointestinal tract
H	Hydroxizine
HRQOL	Health-related quality-of-life
HTD	Human therapeutic dose
IAR	Intermittent allergic rhinitis
ICAM-1	Intracellular adhesion molecule
IgE	Immunoglobulin E
ITT	Intention-to-treat
IV	Intravenous
JRQLQ	Japan Rhinoconjunctivitis Quality-of-Life Questionnaire
K	Ketotifen
L, LRTD	Loratadine
LCTZ	Levocetirizine
M	Monolukast
MAOI	Monoamine oxidase inhibitor
MSC	Major symptom complex
MSCA	McCarthy Scales of Children's Ability
NIH	National Institute of Health
NNSS	Nonnasal symptom
nPEFR	Nasal peak expiratory flow rate
NR	Not reported
NS	Not significant
NSD	Nasal septum deviation
O	Oxatomide
OTC	Over the counter
P, PBO	Placebo
PAR	Perennial allergic rhinitis
PEF	Peak expiratory flow
PR	Precertification
PRQLQ	Pediatric Rhinoconjunctivitis Quality-of-Life Questionnaire
Pts	Patients
qam	Dosing once every morning
QD	Dosing once daily
QoL	Quality-of-life
QTc	QT interval corrected for rate
RAST	Radioallergosorbent test
RCT	Randomized clinical trials
RQLQ	Rhinoconjunctivitis quality of life questionnaire
RR	Relative risk
SAR	Seasonal allergic rhinitis
SCORAD	SCORing Atopic Dermatitis
SD	Standard deviation
SEM	Standard error of the mean
T	Terfenadine
TDSS	Total daily symptom score
TID	Dosing three times daily
TNSS	Total nasal symptom score
TOSS	Total ocular symptom score
TSC	Total symptom complex
TSS	Total symptom score
URI	Upper respiratory infection
URTI	Upper respiratory tract infection
VAS	Visual analog scale
VQ-Dermato	French-language scoring instrument
VR	Ventricular rate
WPAI-AS	Work Productivity and Activity Impairment-Allergy Specific

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
Placebo-controlled trials		
Bachert 2009 Belgium, Bulgaria, France, Germany, Poland, Portugal, Romania and Spain	DB RCT Multicenter	SAR Male and female ,12–70 years, with a documented history of SAR for at least 2 years and a positive skin prick test (wheal ≥ 3 mm larger than the diluent control) to at least one seasonal allergen specific to their geographical location. Patients with a positive prick test to perennial allergens , but without any symptoms of PAR were also enrolled. All patients were additionally required to have a minimum reflective nasal symptom (NSS) score of ≥ 36 as sum of the six assessments in the last 3 days of the screening period
Bernstein 2009	Randomized, double-blind, parallel-group	Male and female patients 12 years of age with a minimum 2-year history of SAR and a positive skin test to a relevant seasonal allergen within the past 12 months were eligible for the trial, A.M. or P.M. 12-hour reflective TNSS of at least 8 of a possible 12 on at least 3 assessments during the lead-in period with an A.M. or P.M. congestion score of at least 2 on at least 3 assessments. For both TNSS and nasal congestion, one of the three assessments selected must have occurred within 2 days of study day 1.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Placebo-controlled trials			
Bachert 2009 Belgium, Bulgaria, France, Germany, Poland, Portugal, Romania and Spain	Hypersensitivity to H1 antihistamines or benzimidazoles and those taking specific H1 or H2 antihistamines within 3 days to 6 weeks; systemic or intranasal corticosteroids within 4 weeks; and intranasal and systemic decongestants within 3 days, immunotherapy (unless on a stable dose within the prior month, and none within 24 h before any study visit) or any CNS acting agents at any time; undergone nasal surgery in the previous 6 months and patients with nasal polyps, significant deviation of the nasal septum, acute or chronic sinusitis, any clinically significant condition (cardiovascular, neurological, hepatic, renal or malignant diseases), a history of alcohol abuse, and pregnant or lactating women	Mean 30 years old 51% male 99% Caucasian	Bilastine 20 mg, desloratadine 5 mg or matched placebo once daily
Bernstein 2009	Any medical or surgical condition or use of concomitant medication(s) that could affect the evaluation of efficacy and safety; pregnant or nursing	Mean age 35 yrs 40% male Ethnicity NR	(1) original azelastine nasal spray, 1 spray/nostril b.i.d.; (2) reformulated azelastine, 1 spray/nostril b.i.d.; (3) placebo, 1 spray/ nostril b.i.d.; (4) original azelastine nasal spray, 2 sprays/nostril b.i.d., (5) reformulated, 2 sprays/nostril b.i.d.; and (6) placebo, 2 sprays/nostril b.i.d.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Placebo-controlled trials			
Bachert 2009 Belgium, Bulgaria, France, Germany, Poland, Portugal, Romania and Spain	NR but "...concomitant medication was noted."	Total symptom score (TSS), which was composed of nasal and nonnasal symptom scores (NSS and NNSS, respectively) recorded by the patient from baseline (day 0) to the end of treatment (day 14) and assessment of NSS and NNSS, QOL assessed by the RQLQ, overall assessment of discomfort due to rhinitis, and the investigators global clinical impression (CGI).	40/1/720
Bernstein 2009	All concomitant medications were discontinued for protocol-specified times based on the elimination half-life	Patient diaries recorded 2x a day- the change from baseline in the 12-hour reflective TNSS over the entire 2 weeks of treatment	20/NR/834

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Placebo-controlled trials	
Bachert 2009 Belgium, Bulgaria, France, Germany, Poland, Portugal, Romania and Spain	Placebo vs. Bilastine vs. Desloratadine Total symptoms score (TSS) AUC TSS 118.4 (62.7) [110.5–126.3] vs. 98.4 (58.1) [90.9–105.9] vs. 100.5 (54.6) [93.6–107.4] P < 0.001 % Change from baseline at day 7 -28.3 (47.4) vs. -41.7 (36.4) vs. -42.9 (35.1) P < 0.001 % Change from baseline at day 14 –37.4 (47.0) vs.-48.9 (38.6) vs. -49.5 (38.8) P = 0.002 Nasal symptoms score (NSS) AUC NSS 71.6 (32.9) [67.4–75.7] vs. 62.6 (32.8) [58.3–66.8] vs. 63.8 (29.7) [60.1–67.6] P = 0.004 % Change from baseline at day 7 -26.4 (50.2) vs. -41.1 (38.6) vs. -45.0 (35.5) P < 0.001 % Change from baseline at day 14 -38.4 (46.6) vs. -48.3 (38.6) vs. -51.9 (39.0) P < 0.001 Non-nasal symptoms score (NNSS) AUC NNSS 47.2 (35.6) vs. 36.5 (29.8) vs. 37.2 (30.8) P < 0.001 % Change from baseline at day 7 -24.2 (78.4) vs. -39.6 (47.9) vs. -36.8 (54.5) P = 0.019 % Change from baseline at day 14 -29.6 (69.2) vs. -47.1 (56.7) vs. -43.7 (49.0) P = 0.003 Total RQLQ -1.3 (1.3) vs. -1.6 (1.2) vs. -1.6 (1.2) P = 0.005
Bernstein 2009	Changes from baseline in the TNSS in the 2-sprays/nostril dosage groups were 27.9% (p<0.001) with the reformulated nasal spray, 23.5% (P<0.01) with the original formulation, and 15.4% with placebo. Change from baseline (sd) / % (sd) P vs. placebo 12-hour reflective total nasal symptom scores 1 spray/nostril b.i.d. Astelin 4.0 (4.56) vs. placebo P = 0.400 / 21.1% (25.89) P = 0.469 Astepro 4.2 (4.61) P = 0.200 / 22.9% (25.74) P = 0.186 Placebo 3.6 (4.57) / 19.0% (24.02) 2 sprays/nostril b.i.d. Astelin 4.2 (4.46) P = 0.008 / 23.5% (25.26) P = 0.008 Astepro 5.1 (4.96) P < 0.001 /27.9% (26.92) P < 0.001 Placebo 18.2 (2.80) / 15.4% (23.05) RQLQ - overall RQLQ score was statistically improved at day 14 compared with placebo with original azelastine nasal spray (P = 0.042) and reformulated azelastine nasal spray (P < 0.001) with the 2-sprays/nostril b.i.d. dosage. 0.55 mean difference in the overall RQLQ score between reformulated 2 sprays/nostril b.i.d. (1.43) and placebo (0.88)

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
LaForce 1996 USA	DB RCT Multicenter (5)	12 years of age or older with histories and diagnoses of seasonal allergic rhinitis that required pharmacologic therapy each year for at least the preceding 2 years. All subjects demonstrated allergy to at least one of the common prevalent seasonal allergens (at the time of the study's conduct) as confirmed by a recognized scratch/prick skin test (at least moderate reaction) within the last year The sum of the scores for sneezes, runny nose/sniffles, nose blows, itchy nose, and watery eyes was to be at least 10 on any four days of the 1-week, prestudy period with at least one of the symptoms of moderate or greater intensity on each of the four qualifying days.
Lumry 2007 USA	2 studies DB RCTs	12 years and older with a minimum 2-year history of SAR and a positive skin test reaction to spring pollen in the previous year

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
LaForce 1996 USA	Clinically significant nasal anatomical deformities (septal defects, polyps), abnormal prestudy laboratory test(s) considered to be clinically significant by the physician, or demonstrated an inability to use or tolerate nasal spray; an episode of acute sinusitis within 30 days or were receiving a changing immunotherapy regimen or scheduled to begin immunotherapy.	Mean age 30 yrs 58% male 82% white	azelastine, 2 sprays/nostril qd; azelastine, 2 sprays/nostril bid; oral chlorpheniramine maleate, 12 mg bid; placebo 4 weeks
Lumry 2007 USA	Any investigational drug within 4 weeks of day 7, and no investigational products were permitted during the studies, evidence of hypersensitivity to drugs similar to azelastine; pregnancy or lactation; women of childbearing potential not practicing a medically acceptable method of contraception; any surgical or medical condition that might significantly alter absorption, distribution, metabolism, or excretion of the study drug; long-term use of concomitant medications that would affect evaluation of the study medications; other nasal disease(s) likely to affect deposition of intranasal medication; presence or history of ocular herpes simplex, cataracts, or glaucoma; respiratory tract infections within 2 weeks of baseline; infections requiring oral antibiotic drug therapy 2 weeks; significant pulmonary disease or active asthma requiring daily medication; a history of or current alcohol or drug abuse; and planned travel outside the study area for a substantial portion of the study period.	Mean age 35 37% male 75% white 14% black 3% Asian 8% other	Azelastine nasal spray, 1 spray per nostril twice daily vs. placebo nasal spray, 1 spray per nostril twice daily, 2 weeks

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
LaForce 1996 USA	Use of inhaled steroids, intranasal or ocular cromolyn, calcium channel blockers, beta blockers, reserpine, or monoamine oxidase inhibitors within 14 days of baseline visit the use of astemizole within 60 days.	Patient diaries and patint and physician grading weekly	30/1/263
Lumry 2007 USA	See exclusion criteria	Patient diaries - change in TNSS from baseline to day 14. change from baseline to day 14 in individual symptoms, patient global evaluation scores, and change from baseline to day 14 in quality of life using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).	12/3/554

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
LaForce 1996 USA	Azelastine 2 sprays qd vs.azelastine 2 sprays bid vs placebo Physicians rated improvement 66.2% vs.78.5% vs. 60.9%; azelastine 2 spray bid vs placebo P ≤ 0.024 Patient rated impovement 75.4% vs. 78.5% vs. 59.4%; azelastine 2 spray bid vs placebo P < 0.024
Lumry 2007 USA	Azelastine vs. Placebo Improvement from baseline TNSS Study 1 2.69 (4.79) vs. 1.31 (4.29) P = 0.01 Study 2 3.68 (4.16) vs. 2.50 (4.01) P = 0.02 Congestion Study 1 0.52 (1.34) vs. 0.40 (1.11) P = 0.42 Study 2 0.89 (1.13) vs. 0.54 (1.16) P = 0.01 Sneezing Study 1 0.82 (1.39) vs. 0.26 (1.29) P < 0.001 Study 2 0.99 (1.17) vs. 0.67 (1.14) P = 0.02 Itchy nose Study 0.72 (1.32) vs. 0.36 (1.21) P = 0.02 Study 2 0.95 (1.22) vs. 0.65 (1.18) P = 0.04 Runny nose Study 1 0.63 (1.37) vs. 0.29 (1.23) P = 0.03 Study 2 0.85 (1.26) vs. 0.63 (1.20) P = 0.14

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
Mahmoud 2008 Kuwait	Observational with placebo control Single center	SAR Typical clinical history and clinical features for at least 3 consecutive pollen seasons in Kuwait, confirmed by a positive skin prick test (SPT) to one or more of local pollen allergen
Meltzer 2005 USA	DB RCT Multicenter	SAR 12 years or older with a history of SAR for at least the preceding 2 years. All the patients demonstrated allergic sensitivity to a prevalent fall allergen as defined by a positive reaction on skin prick testing (a wheal size 3 mm greater than the diluent) or intradermal testing (a wheal size 7 mm greater than the diluent)
Meltzer 2006 USA	DB RCT Single center	Mild-to-moderate SAR for at least 2 years, a positive skin test reaction to a seasonal allergen (including seasonal molds)

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Mahmoud 2008 Kuwait	Acute and chronic upper respiratory infections within 30 days, anatomic nasal disorders (i.e., septum deviation), nasal polyps, and those using antibiotics, nasal, or oral corticosteroids within the previous 4 weeks or antihistamines within the previous week	Mean 31.1 yrs 55% male Rthnicity NR	Levocetirizine vs. placebo 4 weeks
Meltzer 2005 USA	Aberrant nasal anatomy, abnormal prestudy laboratory test results, severe obstructing congestion, recent sinusitis, or abnormal 12-lead electrocardiographic or other abnormal cardiovascular values were excluded from study participation.	Mean age 35 38.2% male 75.6% white 11.5% black 10.6 Hispanic 1.1% Asian 1.2% other	Olopatadine nasal spray vs placebo 2 weeks
Meltzer 2006 USA	Unstable asthma, nasal polyps or nasal anatomic malformations, or a history of clinically significant sinusitis or chronic purulent postnasal drip, incipient or active sinusitis or a respiratory tract infection within 2 weeks of screening,pregnant or nursing women, previous history of an idiosyncratic drug reaction to antihistamines or a history of multiple drug reactions.	Mean age 32 yrs 41% male 63% white 11% black 19% Hispanic 4.6% Asian 1.8% other	Desloratadine and placebo 2 weeks

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Mahmoud 2008 Kuwait	See exclusion criteria	The following symptoms were assessed before and after: sneezing, running and itchy nose, and nasal congestion using a scale: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe.	0/0/20
Meltzer 2005 USA	Medication washout times were 30 days for systemic, inhaled, and ocular corticosteroids; 14 days for intranasal corticosteroids, systemic antibiotics and antihistamines, leukotriene inhibitors, anticholinergic agents, and systemic antibiotics; 7 days for ocular antiallergy agents; 3 days for oral decongestants and nonsteroidal anti-inflammatory agents; and 1 day for nasal and ocular saline. Patients who had undergone previous immunotherapy were required to be stable for 30 days before and throughout.	Patient diaries - the percentage change from baseline in the reflective TNSS, defined as the average of the morning and bedtime reflective severity scores for the sum of the patients' assessments of runny nose, stuffy nose, itchy nose, and sneezing (averaged across all days), percentage change from baseline in the instantaneous TNSS, individual symptoms (ie, runny nose, itchy nose, sneezing, stuffy nose, watery eyes, and itchy eyes), and quality of life (QoL).	NR/NR/565
Meltzer 2006 USA	Suitable washout periods had to be observed for concomitant medications, including other antihistamines, local or systemic corticosteroids, cromolyn, decongestants, leukotriene inhibitors, and inhibitors of cytochrome P450 3A4, oral or long-acting inhaled sympathomimetic bronchodilators was not permitted, stable intermittent asthma were permitted to use inhaled albuterol as required. The use of any investigational product within 30 days was prohibited.	Patient-rated SAR symptoms were recorded twice daily (morning and evening). On days 1 and 15, SAR symptoms were scored jointly (investigator and patient), nasal airflow was measured using 4-phase rhinomanometry, and QOL.	8/1/218

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Mahmoud 2008 Kuwait	Data reported in graphs. Levocetirizine vs. placebo sneezing (P<0.001), nasal itching (P<0.01), nasal congestion, and running nose (P<0.001); reduced percentages of eosinophils (P<0.05); and three subpopulations of activated T lymphocytes: CD4+CD29+, CD4+CD212+, and CD4+CD54+ (P<0.05).
Meltzer 2005 USA	0.6% Olopatadine vs. 0.4% Olopatadine vs. Placebo P = olopatadine group vs the placebo group. TNSS 39.2(26.9) P < 0001 vs. 35.8 (28.1) P = 0.004 vs. 27.0 (27.8) Runny nose 38.5 (32.0) P < 0.001 vs. 33.0(36.4) P = 0.046 vs. 24.9 (36.3) Stuffy nose 24.5 (77.6) P = 0.85 vs. 25.7(30.1) P = 0.70 vs. 22.0 (30.5) Itchy nose 39.5(32.5) P = 0.001 vs. 38.1(33.3) P = 0.005 vs. 27.8 (34.0) Sneezing 51.7 (32.4) P < 0.001 vs. 49.5(37.6) P = 0.001 vs. 29.0 (51.7) Itchy eyes 41.4 (41.6) P = 0.02 vs. 35.2 (43.1) P = 0.41 vs. 30.2 (40.9) Watery eyes 46.7 (43.1) P = 0.05 vs. 44.3 (40.2) P = 0.17 vs. 37.1 (39.7)
Meltzer 2006 USA	Most data reported in graphs - Desloratadine vs placebo. Total symptom (P = 0.03) and total nasal symptom (P = 0.02) scores and patient morning-rated individual nasal symptom scores (except nasal stuffiness) (P = 0.04) decreased significantly from baseline Flow in the descending expiratory nasal airflow phase was significantly greater (P = 0.046) and the percentage increase in total inspiratory nasal airway resistance was less (P = .03) in the desloratadine group vs the placebo group. Overall condition of SAR was less severe (P = 0.045), the therapeutic response was greater (P = 0.004), and the nasal symptom domain of the QOL score was significantly better (P = 0.03) in the desloratadine group.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
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.
Pradalier 2007 France	DB RCT Multicenter	Aged 18 years or more with at least 2 years history of seasonal AR as confirmed by a positive skin prick test to grass pollen.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Okubo 2004, 2005 Japan	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).	Mean age: 33.5y 58.2% female Ethnicity: NR	F: Fexofenadine 60 mg bid P: placebo bid 14-day treatment period
Pradalier 2007 France	Pregnant/breast-feeding women; women not using acceptable birth control; subjects in the ascending phase of immunotherapy or receiving long-term intranasal corticosteroids within 30 days; requirements for chronic corticosteroids; use of leukotriene inhibitors within 7 days or ketotifen within 14 days prebaseline; dependence on topical/systemic decongestants, topical antihistamines or nasal steroids; current/past history of significant sinusitis or chronic purulent postnasal drip, rhinitis medicamentosa, upper respiratory tract or sinus infection requiring antibiotics 14 days before baseline; viral upper respiratory infection within 7 days or significant nasal structural abnormalities or iInvestigational medications and antibodies were forbidden for 30 and 90 days prebaseline.	Mean age 32.5 yrs 52% male Ethnicity NR	Desloratadine 5 mg or placebo daily for 2 weeks

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Okubo 2004, 2005 Japan	Any concurrent use of drugs that could influence the evaluation of efficacy was prohibited.	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
Pradalier 2007 France	NR	Symptoms scores were recorded at baseline and the end of treatment and also twice daily in patient diaries (AM/PM). Global response to therapy was assessed jointly at visit 3 (day 14) by investigator and patient	NR/NR/483

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
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
Pradalier 2007 France	Placebo vs. Desloratadine (baseline/change) Rhinorrhea 2.15 (0.77) / -0.76 (1.18) vs.2.14 (0.87) / -1.05 (1.21) P = 0.01 Nasal congestion 2.43 (0.50) / -0.78 (1.05) vs. 2.46 (0.50) / -0.97 (1.01) P = 0.054 Sneezing 2.2 (0.74) / -0.87 (1.16) vs. 2.27 (0.73) / -1.33 (1.14) P < 0.0001 Nasal itching 1.85 (0.87) / -0.65 (1.23) vs. 1.8 (0.90) / -0.89 (1.10) P = 0.02 Total Nasal Symptoms 8.63 (1.76) / -3.06 (3.65) vs. 8.67 (1.88) / -4.24 (3.37) P = 0.0003 Eye symptoms 2.04 (0.80) / -0.79 (1.12) vs. 2.09 (0.81) / -1.1 (1.13) P = 0.003 Itchy ears/palate 1.54 (1.00) / -0.63 (1.15) vs.1.55 (1.00) -0.89 (1.11) P = 0.01 Total Non-Nasal Symptoms 3.57 (1.36) / -1.43 (1.90) vs.3.64 (1.30) / -2.00 (1.82) P = 0.001 Total Symptoms Score 12.21 (2.60) / -4.49 (5.09) vs. 12.31 (2.65) / -6.23 (4.66) P = 0.0001 Total RQLQ Score 3.22 (1.04) / -0.72 (1.33) vs. 3.23 (0.94) / -1.20 (1.34) P = 0.0003

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
Ratner 1994 USA	RCT, DB, parallel-group, multi-center (4) in Texas	SAR 12 or more years old; history and diagosis of allergic rhinitis to mountain ceder pollen for at least 2 yrs; confirmed allergy with scratch/prick test within last year
Ratner 2005 USA	Multicenter (7 sites in Texas), randomized, double-blind, parallel-group, placebo-controlled	12 years or older with a history of SAR for at least the preceding 2 years. All the patients demonstrated allergic sensitivity to a prevalent fall allergen defined by a positive reaction on skin prick testing (a wheal size 3 mm greater than the diluent) or intradermal testing (a wheal size 7 mm greater than the diluent)
UCB 2008 Evaluation of the efficacy and safety of levocetirizine during 8 weeks preceeding	DB RCT, multicenter (53)	Male or female, ≥ 12 years of age, with a ≥ 2 year history of seasonal allergic rhinitis that became symptomatic during the annual grass pollen season, a documented hypersensitivity to grass pollen, without an acute ongoing exacerbation of asthma or allergic rhinitis

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Ratner 1994 USA	Pregnant or lactating women; asthma requiring chronic treatment; URTI; clinically significant nasal defects or other significant medical conditions; acute sinusitis in last 30 days; immunotherapy Patients receiving calcium channel blockers, beta blockers, cromolyn; reserpine; MAOIs or inhaled steroids within 14 days; H1 receptor antagonists ordecongestants w/in 48 hrs; systemic seroids w/in 30 days; astemizole w/in 60 days	Mean age 38 yrs 55% male 97% white 3% other	Azelastine 2 sprays per nostril bid, azelastine 2 sprays per nostril qd, chlorpheniramine 12 mg bid, or placebo Duration 2 weeks
Ratner 2005 USA	Aberrant nasal anatomy, abnormal prestudy laboratory test results, severe congestion, recent sinusitis, or abnormal 12-lead electrocardiographic or other abnormal cardiovascular values. Medication washout times - 30 days systemic, inhaled, and ocular corticosteroids; 14 days intranasal corticosteroids, leukotriene inhibitors, anticholinergic agents, and systemic antibiotics; 7 days ocular and nasal antiallergy agents; 3 days oral antihistamines, nonsteroidal anti-inflammatory drugs, and decongestants; and 1 day for nasal and ocular saline	Mean age 39 yrs 33.6% male 64.6% white 29.2% Hispanic 4.4% African American 1.3% Asian 0.4% other	0.6% olopatadine vs. 0.4% olopatadine vs. placebo
UCB 2008 Evaluation of the efficacy and safety of levocetirizine during 8 weeks preceeding	Continuous ongoing treatment for rhinitis or asthma, and a documented pollen-induced asthma (clear exacerbation of symptoms at the grass pollen season) with ≥1 asthma exacerbation over the past 3 years	Mean age 31 yrs 49% male 95% white	Levocetirizine 5 mg/day (LCTZ),vs. placebo (PBO) for 16 weeks 8 wks before pollen season and then 8 more wks, PBO/PBO LCTZ/LCTZ and PBO/LCTZ .

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Ratner 1994 USA	None reported; note exclusion criteria	Changes in Major Symptom Complex (nose blows, sneezes, runny nose/sniffles, itch nose, and watery eyes) and Total Symptom Complex (Major plus itchy eyes/ears/throat/palate, cough, and postnasal drip) severity scores via patient diaries	2/1/250 safety and 249 efficacy
Ratner 2005 USA	Immunotherapy -stable for 30 days before and throughout the trial	Patients recorded in a diary the symptom severity of their itchy nose, runny nose, stuffy nose, sneezing, itchy eyes, and watery eyes using a 4-point scale (0 absent, 1 mild, 2 moderate, and 3 severe). Sum of scores for the 4 nasal symptoms was defined as the total nasal symptom score (TNSS)	NR/NR/675
UCB 2008 Evaluation of the efficacy and safety of levocetirizine during 8 weeks preceeding	NR	Analysis of the Total 4 Symptoms Score (T4SS; sum of the scores of the severity of sneezing, rhinorrhea, nasal pruritus and ocular pruritus).	68/0/303 (3rd arm was not reported on for efficacy)

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Ratner 1994 USA	Azelastinel bid vs. azelastine qd vs. chlorpheniramine vs. placebo Endpoint analyses mean improvement TSC 32% vs. 28% vs. NR vs. 19% (Azelastinel bid vs. placebo statistically significant) MSC 34% vs. 27% vs. NR vs. 20% (Azelastinel bid vs. placebo statistically significant) Investigator rated therapeutically improved 84% (vs. placebo P < 0.05) vs. 73% vs. NR vs. 66% Patient rated therapeutically improved 82% vs. 86% vs. NR vs. 77% Article states that chlorpheniramine was staistically better than placebo but does not provide data outside of graphs
Ratner 2005 USA	0.6% Olopatadine vs. 0.4% Olopatadine vs. Placebo (P = active vs. placebo) **Percentage Change From Baseline in the Reflective Assessments of Symptoms (SD)** TNSS 30.1(27.6) P < 0 .001 vs. 27.6(22.4) P < 0.001 vs. 18.7(22.3) Runny nose 30.0(31.5) P < 0.001 vs. 22.3 (32.4) P = 0.27 vs. 18.4 (24.1) Stuffy nose 21.7 (31.7) P = 0.002 vs. 21.3(24.0) P = 0.004 vs. 13.2 (26.0) Itchy nose 32.4 (32.5) P < 0.001 vs. 30.8(27.5) vs. P < 0.001 vs. 19.4 (38.0) Sneezing 35.7 (38.9) P < 0.001 vs. 33.4 (37.9) P < 0.001 vs. 18.8 (43.4) Itchy eyes 30.7 53.8 P < 0.001 vs. 25.3(41.9) P = 0.008 vs. 12.3 (45.7) Watery eyes 31.9(46.7) P = 0.002 vs. 29.9 (40.3) P = 0.009 vs. 18.0 (43.8) **Percentage Change From Baseline in the Instantaneous Assessments of Symptoms (SD)** TNSS 26.2(29.6) P < 0.001 vs. 24.3 (23.3) P = 0.002 vs. 15.8(26.4) Runny nose 24.6 (38.2) P= 0.005 vs. 20.2(31.1) P= 0.19 vs. 15.4 (26.9) Stuffy nose 17.5(31.9) P = 0.004 vs. 17.0(25.2) P = 0.005 vs. 7.7 (39.2) Itchy nose 30.2 (36.7) P < 0.001 vs 26.7 (34.4) P = 0.005 vs. 15.8 (43.6) Sneezing 29.6 (45.3) P = 0.03 vs. 29.2(60.6) P = 0.03 vs. 16.8 (57.8) Itchy eyes 27.6(64.0) P = 0.008 vs. 21.8(50.5) P = 0.14 vs. 12.9 (41.6) Watery eyes 28.5(54.1) P = 0.07 vs. 24.2(51.3) P = 0.39 vs. 18.4 (46.1)
UCB 2008 Evaluation of the efficacy and safety of levocetirizine during 8 weeks preceeding	LCTZ/LCTZ vs. PBO/PBO Comparison of mean T4SS over the first 12 weeks of the study (SD) 2.25 (1.72) vs. 1.64 (1.80) Difference in adjusted mean (95% CI), LCTZ/LCTZ vs PBO/PBO 0.65 (0.27,1.03) P < 0.001

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
Active-control trials		
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.
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.
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.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Active-control trials			
Bernstein 2004 USA	NR	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
Bhatia 2005 USA	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	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
Dockhorn 1987 USA	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.	Age: 32, range 12-65 79% male 93% white	L: loratadine 10 mg C: clemastine 2 mg P: placebo

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Active-control trials			
Bernstein 2004 USA	No	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	Acetaminophen, birth control pills, Depo-Provera, or as-needed bronchodilators only	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
Dockhorn 1987 USA	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.	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
Active-control trials	
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
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
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.
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.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Hampel 2004 USA	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.	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
Martinez-Cocera 2005 Spain	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	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

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Hampel 2004 USA	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.	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	No (Pt had to report any concomitant meds that are not listed in exclusion criteria)	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
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
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
Storms 1994 USA	RCT, DB, parallel-group, multi-center	SAR 12 or more years old; history and diagosis of seasonal SAR for at least 2 yrs; confirmed allergy with scratch/prick test within last year

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Ratner 2004 USA	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	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.
Saint-Martin 2004 France	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.	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
Storms 1994 USA	Pregnant or lactating women; asthma requiring chronic treatment; URTI; clinically significant nasal defects or other significant medical conditions; acute sinusitis in last 30 days; immunotherapy Patients receiving calcium channel blockers, beta blockers, cromolyn; reserpine; MAOIs or inhaled steroids within 14 days; H1 receptor antagonists ordecongestants w/in 48 hrs; systemic seroids w/in 30 days; astemizole w/in 60 days	Mean age 32 yrs 55% male 89% white	Azelastine 2 sprays per nostril bid, azelastine 2 sprays per nostril qd, chlorpheniramine 12 mg bid, or placebo Duration 2 weeks

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Ratner 2004 USA	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.	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	None reported; note exclusion criteria	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
Storms 1994 USA	None reported; note exclusion criteria	Changes in Major Symptom Complex (nose blows, sneezes, runny nose/sniffles, itch nose, and watery eyes) and Total Symptom Complex (Major plus itchy eyes/ears/throat/palate, cough, and postnasal drip) severity scores via patient diaries	2/2/245

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)
Storms 1994 USA	Azelastinel bid vs. azelastine qd vs. chlorpheniramine vs. placebo Endpoint analyses mean improvement TSC 28% vs. 15% vs. NR vs. 8% (Azelastinel bid and. azelastine qd vs. placebo P $\leq$ 0.005) MSC 29% vs. 14% vs. NR vs. 8% (Azelastinel bid and. azelastine qd vs. placebo P < 0.005) Investigator rated therapeutically improved 84% (vs. placebo P < 0.01) vs. 80% (vs. placebo P = 0.01) vs. NR vs. 54% Patient rated therapeutically improved 84% (vs. placebo P $\leq$ 0.01) vs. 80% (vs. placebo P = 0.01) vs. NR vs. 59% Article states that chlorpheniramine was staistically better than placebo but does not provide data outside of graphs

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
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

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
van Adelsberg 2003 USA	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	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

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
van Adelsberg 2003 USA	Short-acting B-agonists for asthma	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
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
Head-to-head 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.
Berger 2006 USA	DB RCT Multicenter (34)	SAR 12 years or more , history of SAR for at least 2 years; positive skin test to prevalent aeroallergen
Berger 2006 USA	DB, RCT Multicenter (24)	SAR males and females 12 years and older with at least a 2-year history of SAR and a documented positive skin test reaction to ambient pollen aeroallergen during the previous year.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Head-to-head trials			
Berger 2003 USA	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.	Age: 35, range 12-79 66% female 80% white	D: desloratadine 5 mg A1: azelastine nasal A2: azelastine nasal + loratadine P: placebo
Berger 2006 USA	2 or more episodes in past year of clinically significant sinusitis, chronic post nasal drip; ongoing rhinitis; nasal polyps easily visible; marked septum deviation; URTI; requring antibiotic treatment; serious concomitant disease	34.7 years old 34% male 90% white 17% black 3% other 3.5% hispanic	Fexofenadine 180 mg vs. desloratadine 5 mg vs. placebo 15 day duration
Berger 2006 USA	Use of concomitant medication(s) that could affect the evaluation of efficacy; any medical or surgical condition that could affect the metabolism of the study medications; clinically significant nasal disease (other than SAR) or significant nasal structural abnormalities; respiratory tract infection or other infection requiring antibiotic drug therapy within 2 weeks; a history of or current alcohol or other drug abuse; or significant pulmonary disease, including persistent asthma requiring daily controller medication; women of childbearing potential not using an accepted method of contraception and women who were pregnant or nursing.	Mean age, 35 years 42% male 78% white 7% black 5% Asian 10% other	Azelastine, 2 sprays per nostril twice daily, vs. cetirizine, 10-mg tablets once daily. Duration 14 days

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Head-to-head trials			
Berger 2003 USA	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.	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
Berger 2006 USA	None were allowed that would interfere with treatment ofSAR	Patient diary daily 2x, AM symptoms, immediate and in past 12 hours, and the same thing in the evening, with the exception of congestion and investigator/subject joint evaluation of therapeutic response at days 8 and 15	28/2/643 Per protocal analysis
Berger 2006 USA	NR	Change from baseline to day 14 in rhinitis symptom severity based on the combined morning and evening 12-hour reflective TNSS, secondary efficacy variables were (1) change from baseline to day 14 in QoL variables using the RQLQ and (2) change from baseline to day 14 in individual symptoms	18/2/354

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
Head-to-head 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%
Berger 2006 USA	Fexofenadine vs. desloratadine vs. placebo investigator/subject joint evaluation of therapeutic response moderate/complete symptom relief 8 days 58% (vs. placebo P=0.019) vs. 58% (vs. placebo P=0.009) vs. 45% 15 days 59% vs. 59% vs. 51% Mean AM NOW TSSs at day 15 with desloratadine (P=0.006) and fexofenadine (P=0.024) versus placebo Decrease in mean AM/PM PRIOR TSS excluding congestion between desloratadine and fexofenadine (P=0.405) vs. placebo (desloratadine, P=0.001; fexofenadine, P=0.003).
Berger 2006 USA	Azelastine vs. Cetirizine mean (SD) Improvement in TNSS was 4.6 (4.2) vs. 3.9 (4.3) P = 0.14 Percentage change 23.9% vs. 19.6% P = 0.08 RQLQ nasal symptoms P $\leq$ 0.05 Overall RQLQ score P = 0.002 TNSS subscores Nasal congestion P = 0.049 Sneezing P = 0.01 Most data reported in graphs

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
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.
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.
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.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Ciprandi 1997 Italy	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.	Age: 31 years, range 18-44 38% female	L: loratadine 10 mg qd C: cetirizine 10 mg qd
Corren 2005 USA	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.	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
Hampel 2003 US	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.	Age: 34.8 years, range 12-70 66% female 67% Caucasian	F: fexofenadine 180 mg qd C: cetirizine 10 mg qd

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Ciprandi 1997 Italy	No medication that would affect the disease were permitted.	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
Corren 2005 USA	No	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
Hampel 2003 US	NR	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

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
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.
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
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.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
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.
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).
Shah 2009 USA	Multicenter (21), randomized, double-blind, active- and placebo-controlled, parallel group	12 years or more ; who had a 2-year history of spring or fall allergic rhinitis; were allergic to the prevalent seasonal allergen in their geographic area, as confirmed by a positive case history and skin prick or transdermal test; and had a total nasal symptom score (TNSS) of a threshold level.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Howarth 1999 UK, US, France	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.	Age: 33 years 51% male	F1: fexofenadine 120 mg qd F2: fexofenadine 180 mg qd C: cetirizine 10 mg qd P: placebo
Prenner 2000 US	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.	Age: 35.3 years (fexofenadine), 32.3 years (loratadine) 60% female	L: loratadine 10 mg qd F: fexofenadine 120 mg qd
Shah 2009 USA	Concurrent diseases that might have interfered with the evaluation of the effects of the study medication; a history of chronic sinusitis; asthma more severe than mild intermittent asthma; congestion that might have interfered with drug administration; or a clinically significant anatomic abnormality, infection, bleeding, or mucosal ulceration of the nose; known nonresponders to antihistamines for SAR symptoms or used any of the following : a long-acting antihistamine long-term; or an inhaled, oral, 1M, IV, or dermal potent or superpotent topical corticosteroid intermittently or long-term.	Mean age 54 yrs 32.2% male 75.4% white 12.1% Hispanic 11.4% black 0.7% Asian 0.4% "other"	Olopatadine hydrochloride nasal spray 0.6% (OLO) vs. azelastine hydrochloride nasal spray 0.1% (AZE) vs. placebo for 16 days

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Howarth 1999 UK, US, France	NR	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
Prenner 2000 US	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.	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
Shah 2009 USA	Not reported	Daily SAR symptoms in an electronic diary via a personal digital assistant and RQLQ at end, 16 day duration of tratment	NR/NR/544

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
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)
Prenner 2000 US	TSS, Patient assessment: L: -39% F: -33% (p=0.019) TSS, Investigator assessment: L: -35% F: -29% (p=0.063)
Shah 2009 USA	Change in TNSS OLO 26.8% (mean baseline score, 8.8; mean diary period score, 6.4) vs. placebo 18.4% (mean baseline score, 8.4; mean diary period score, 6.7) (Placebo vs OLO P = 0.003) vs. AZE 29.9% (mean baseline score, 8.8; mean diary period score, 6.2); difference between active treatments was nonsignificant (95% CI, -2.5% to 8.7%). RQLQ mean change in overall score significantly greater with OLO vs. placebo (P = 0.005); not significantly different versus AZE Other data reported in graphs

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
UCB 2007 Multicenter, double-blind, parallel, randomized, placebo-controlled study: evaluation of the efficacy and safety of levocetirizine 5 mg and desloratadine 5 mg	DB RCT Multicenter	Male or female subjects aged ≥18 years, with a 2-year clinical history of AR and a minimum mean T4SS of 6 over the 3- to 7-day baseline period
UCB 2008 A monocenter, double-blind, randomized trial	DB RCT, single center	Adult subjects suffering from seasonal allergic rhinitis (SAR) due to grass pollen
UCB 2008 "Study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of seasonal allergic rhinitis (SAR)	DB RCT 2 centers	Male and female, aged 18 to 60 years, clinically diagnosed with SAR, with a mean T5SS of ≥ 5 evaluated the last 24 hours of the selection week and the day before the randomization visit

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
UCB 2007 Multicenter, double-blind, parallel, randomized, placebo-controlled study: evaluation of the efficacy and safety of levocetirizine 5 mg and desloratadine 5 mg	NR	Mean age 34 yrs 44% male 92.5% Caucasian	PBO vs. DESL 5 mg vs. LCTZ 5 mg
UCB 2008 A monocenter, double-blind, randomized trial	NR	Mean age 34 yrs 51.5% male 99.5% white	Levocetirizine 5 mg capsules vs. desloratadine 5 mg capsules 1 to 3 weeks
UCB 2008 "Study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of seasonal allergic rhinitis (SAR)	NR	Mean age 37.4 yrs 60% male 100% Mongolian / Asian	Levocetirizine (LCTZ 5 mg) compared to loratadine (LRTD 10 mg)

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
UCB 2007 Multicenter, double-blind, parallel, randomized, placebo-controlled study: evaluation of the efficacy and safety of levocetirizine 5 mg and desloratadine 5 mg	NR	Mean change from the baseline of Total 4 Symptom Score (T4SS) over 2 weeks of treatment (T4SS: sum of the individual symptom scores for sneezing, rhinorrhea, nasal pruritus, and ocular pruritus, evaluated on a 4-point scale retrospectively over the past 24 hours)	60/NR/765
UCB 2008 A monocenter, double-blind, randomized trial	NR	Patient diary, Subjects' satisfaction/dissatisfaction after the first week of treatment (subject's choice to continue with the administered treatment or to switch to alternative treatment); correlation between switch and various aspects of the T5SS (sum of individual symptom scores for sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion evaluated on a 4- point scale retrospectively over the past 24 hours); subject satisfaction/dissatisfaction.	4/NR/NR (96 or 100)
UCB 2008 "Study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of seasonal allergic rhinitis (SAR)	NR	Change of investigator assessed T5SS, from baseline to end of treatment (14 days).	1/0/67

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Results
UCB 2007 Multicenter, double-blind, parallel, randomized, placebo-controlled study: evaluation of the efficacy and safety of levocetirizine 5 mg and desloratadine 5 mg	T4SS The difference between DESL 5 mg and LCTZ 5 mg 0.3 95% CI [-0.06; 0.66]. P = 0.102
UCB 2008 A monocenter, double-blind, randomized trial	No quatitative results reported or statistics, just trends that were noticed. No difference between the LCTZ 5 mg and DESL 5 mg treatment groups in the percentage of subjects who switched to alternative treatment during the study. A more pronounced improvement of T5SS, during 1 week, in subjects treated with LCTZ 5 mg compared to subjects treated with DESL 5 mg Faster overall symptom relief, faster blocked nose relief, higher satisfaction with quality of sleep and daily activities, and better blocked nose relief in subjects treated with LCTZ 5 mg.
UCB 2008 "Study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of seasonal allergic rhinitis (SAR)	Least Square (LS) mean changes from baseline of T5SS was –5.54 for LCTZ group and –5.99 for LRTD group, the difference between the two treatment groups was not statistically significant (p=0.4798).

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Study design Setting	Population Eligibility criteria
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.

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Exclusion criteria	Age Gender Ethnicity	Interventions
Van Cauwenberge 2000 Europe and South Africa	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.	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

Evidence Table 1. Seasonal allergic rhinitis trials in adults

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Number withdrawn/ lost to follow-up/analyzed
Van Cauwenberge 2000 Europe and South Africa	Systemic or nasal corticosteroids, nedocromil or cromolyn sodium, oxatomide, oral or nasal decongestants, alpha adrenergic drugs, or other antihistamines were prohibited.	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
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
Berger 2006 Efficacy	Yes	NR	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes
Berger 2006 Impact	Yes	Yes	NR	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes
Bachert 2009	Yes	NR	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes
Bernstein 2004	Method not reported	Method not reported	Yes	Yes	Yes	Yes	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
Berger 2003	NR	No	Yes	Yes	Manufacturer funded	Fair
Berger 2006 Efficacy	Attrition reported (4%); crossover, adherence, contamination NR	No	No Not all randomized were in ITT (643/722 in some analyses)	No	Integrated Therapeutics Group, Inc. (a subsidy of Schering-Plough)	Fair
Berger 2006 Impact	Attrition reported (3.5%); crossover, adherence, contamination NR	No	No 354/360 in ITT	No	MedPointe Pharmaceuticals	Fair
Bachert 2009	Attrition reported (6%);no crossover; adherence 100%; contamination NR	No	Yes	No	FAES FARMA, S.A., Spain	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

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?**
Bernstein 2009	Yes	Method not reported	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	NR; study reported as "double blind"
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

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
Bernstein 2009	Attrition reported (2.4%)	No	No 843/835 in ITT		NR J. Bernstein, B. Prenner, B. Ferguson, and J. Portnoy receive grant/research support from Meda Pharmaceuticals. J. Bernstein, B. Prenner, and B. Ferguson are consultants for Meda Pharmaceuticals. J. Bernstein and B. Prenner are also speakers for Meda Pharmaceuticals. W. Wheeler and H. Sacks are employees of Meda Pharmaceuticals	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

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?**
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)
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

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
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.
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

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?**
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
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
LaForce 1996	NR	NR	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes; identical placebo given
Lumry 2007	NR	NR	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	NR; study reported as "double blind"
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

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
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
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.
LaForce 1996	Attrition reported (30/264 dropped), others NR	No	Yes	No	NR	Fair
Lumry 2007	Attrition reported (12/554 dropped), others NR	No	Yes	2 were withdrawn for being noncompliant with protocol	Medpointe Pharmaceuticals	Fair
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

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?**
Meltzer 2005	NR	NR	Yes	Yes	Unclear: stated as "double blind"	Unclear: stated as "double blind"	Unclear: stated as "double blind"
Meltzer 2006	NR	NR	Yes	Yes	Unclear: stated as "double blind"	Unclear: stated as "double blind"	Unclear: stated as "double blind"
Mahmoud 2008	NR	NR	Yes	Yes	Unclear	Unclear	Unclear
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"
Pradalier 2006	Yes	NR	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
Meltzer 2005	No/No/No/No	Unclear	Yes	No	Alcon Research	Fair
Meltzer 2006	Yes/No/No/No	No/No	Yes	No	Schering-Plough Corp., France	Fair
Mahmoud 2008	No/No/No/No	Unclear	NR	NR	NR	Poor
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
Pradalier 2006	NR Not clearly reported	NR	No 483/534 in ITT	Yes 51/534 (9.6%) excluded for not meeting inclusion criteria	Schering-Plough Corp., France	Fair
Prenner 2000	NR	No	Yes	No	Manufacturer funded	Fair

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"
Shah 2009	Yes; Computer generated and blocked	Yes	Yes	Yes	Yes	Yes	Yes
Storms 1994	NR	NR	Yes	Yes	NR; stated "double dummy"	NR; stated "double dummy"	Yes; identical placebo given
Ratner 1994	NR	NR	No statistical difference, but more men in azelastine NS bid group compared to other groups	Yes	NR; stated "double dummy"	NR; stated "double dummy"	Yes; identical placebo given

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
Shah 2009	Reports withdrawals based on AEs but others NR	Unclear	Modified ITT	Unclear	Alcon Research Ltd	Fair
Storms 1994	Attrition reported (2/245 dropped), others NR	No	Yes	No	NR	Fair
Ratner 1994	Attrition reported (2/251 dropped), others no	No	Yes	No	Wallace laboratories	Fair

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 2005	NR	NR	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes; identical placebo given
UCB NCT00160537, A monocenter, double-blind…	Method not described	Not described	NR	Yes	Unclear, described as double blind	Unclear, described as double blind	Unclear, described as double blind
UCB, NCT00160589, A multicentre, double-blind…	Method not described	Not described	NR	Yes	Unclear, described as double blind	Unclear, described as double blind	Unclear, described as double blind
UCB NCT00525278, Study evaluating the efficacy…	Method not described	Not described	NR	Yes	Unclear, described as investigator blinded	Unclear, described as investigator blinded	Unclear, described as investigator blinded
UCB, NCT00521040, Evaluation of the efficacy…	Method not described	Not described	NR	Yes	Unclear, described as double blind	Unclear, described as double blind	Unclear, described 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 2005	NR; but analysis done on whole group	NR	Yes	Yes; 2 patients withdrawn because they enrolled at 2 sites	Alcon Research Ltd	Fair
UCB NCT00160537, A monocenter, double-blind…	Attrition reported, none of others reported	No	Unclear, but low attrition	No	UCB	Fair
UCB, NCT00160589, A multicentre, double-blind…	Attrition reported, none of others reported	More dropouts in placebo group	Yes	No	UCB	Fair
UCB NCT00525278, Study evaluating the efficacy…	Attrition reported, none of others reported	No	Unclear, but low attrition	No	UCB	Fair
UCB, NCT00521040, Evaluation of the efficacy…	Attrition reported, none of others reported	yes, 85%	No, 3 patients excluded from analysis	Unclear	UCB	Poor
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

	Internal validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
van Cauwenberge 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
van Cauwenberge 2000	Yes/No/No/Yes	No	Yes	Yes	Manufacturer funded	Fair

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Bachert 2004 Persistant Allergic Rhinitis Trial name XPERT Multinational - Belgium, France, Germany, Italy, and Spain Canonica 2006 Klimek 2007	DB RCT Multicenter	PER symptoms (i.e. rhinitis 4 days a week for 4 or more consecutive weeks) and sensitized to both house mites and pollen	Pregnant patients, nursing mothers, and women of childbearing age not using a medically accepted method of contraception; ear, nose, or throat or eye infection during the 2 weeks preceding the initial visit, and patients with asthma requiring daily treatment with other than an inhaled β-agonist as needed; atopic dermatitis or urticaria requiring antihistamine or corticosteroid treatment; an associated ear, nose, or throat disease such as vasomotor rhinitis or nasal polyps; other clinically significant diseases such as glaucoma or cardiovascular or hepatic diseases; or any condition likely to disturb absorption, distribution, metabolism, or excretion of the investigational drug.

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
Bachert 2004 Persistant Allergic Rhinitis Trial name XPERT Multinational - Belgium, France, Germany, Italy, and Spain Canonica 2006 Klimek 2007	Mean age 30.3 43.7% male Ethnicity NR	Levocetirizine 5mg or placebo once daily for 6 months	Nasal or ocular cromolyn and prednisolone	Symptoms, HRQOL and health status via electronic patient diary	131/1/551

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
Bachert 2004 Persistant Allergic Rhinitis Trial name XPERT Multinational - Belgium, France, Germany, Italy, and Spain	Most data in graphs. Levocetirizine vs.placebo in HRQOL (P < 0.001 for all RQLQ domains and overall scores) and health status (P < or = 0.004 for SF-36 physical and mental summary scores; P < 0.05 for all SF-36 scales) Improvement of Levocetirizine over placebo Overall RQLQ 36.4%, activities 38.5%, emotions 37.4%, eye symptoms 40.2%, nasal symptoms 40.3% and sleep 40.8% Mean changes in SF-36 (placebo minus Levocetirizine) Role-physical -9.92 Role-emotional -7.16
Canonica 2006	at 4 weeks mean T5SS levocetirizine versus placebo (−3.54 vs −2.40), which equates to an adjusted mean difference of 1.14 (P < .001)
Klimek 2007	effect of treatment on 5 RQLQ activities Doing your house work: change from baseline for placebo at 6 months mean, SE: -1.87(0.18) change from baseline for levoceterizine at 6 months: -2.57 (0.18), difference vs placebo 95% CI 0.70 [0.23; 1.16), p=0.003 Playing sport: placebo change from baseline at 6 months: -1.73 (0.20) levoceterizine change from baseline at 6 months: -2.23(0.23), difference vs placebo 95% CI 0.50(-0.07; 1.06), p=NS Driving placebo change from baseline at 6 months -2.49 (0.24) levoceterizine change from baseline at 6 months --2.82 (0.21), difference vs placebo 95% CI 0.34[-0.25; 0.93), p=NS Outdoor activities placebo change from baseline at 6 months -2.20(0.22) levoceterizine change from baseline at 6 months -2.96(0.22), difference vs placebo 0.76 (0.17; 1.35), p=0.011 Carrying out activities at work placebo change from baseline at 6 months -2.14 (0.17) levoceterizine change from baseline: -2.93 (0.17), difference vs placebo 95% CI 0.79 (0.32; 1.26), p<0.001 Difficulty getting sleep placebo change from baseline at 6 months -1.36 (0.09) levoceterizine change from baseline at 6 months -1.70, difference vs placebo 95% CI 0.35(0.10; 0.59), p=0.006 Waking up during the night placebo change from baseline at 6 months: -1.09(0.09), levoceterizine change from baseline at 6 months-1.40 (0.09), difference versus placebo 95% CI 0.31 (0.07; 0.56), p=0.013 Lack of good night's sleep placebo change from baseline at 6 months -1.00(0.09) levoceterizine change from baseline at 6 months -1.50 (0.09), difference vs placebo 95% CI 0.50(0.25; 0.65), p<0.001

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Berlin 2000 USA	Double-blind, placebo-controlled, crossover at single center	PAR Age 18 to 55 years, daytime fatigue, daytime somnolence, nasal congestion, perennial allergic rhinitis with a positive skin test response for perennial allergen (wheal diameter at least 3 mm), and a negative skin test response for seasonal allergens.	Seasonal allergies, known sleep apnea, nasal polyps, obesity, recent upper respiratory tract infection, deviated septum, and asthma or other respiratory diseases
Bruttman 1989	DB cross over study	Suffered from perennial rhinitis for at least one year	Pregnant or child bearing potential under 16 or more than 45 yrs oldchronic non-allergic rhinitis, aspirin induced rhinitis, corticosteroid dependency, hepatic or renal deficiency
Ciprandi 2005 Italy	DB RCT, single center	PAR - males and females aged > 18 years, history of PAR due to perennial allergen exposure for the previous 2 years, rhinitic symptoms in the 2 previous weeks with total symptom score (TSS) ≥ 6 at baseline, particularly with moderate to severe nasal obstruction	Pollen allergy, acute and chronic upper respiratory infections within the previous 30 days, anatomic nasal disorders (i.e., septum deviation), nasal polyps, use of antibiotics, intranasal or oral corticosteroids within the previous 4 weeks, and use of antihistamines during the previous week. Women who were breastfeeding, pregnant, or at risk of becoming so

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
Berlin 2000 USA	Mean age 35 yrs 42% male Ethnicity NR	Azelastine hydrochloride vs. placebo	No	Questionnaires at baseline and every 2 weeks and a daily diary, which focused on nasal symptoms, sleep, and daytime sleepiness. Completers analysis	5/NR/19
Bruttman 1989	29.4 yrs 66% male Ethnicity NR	Cetirizine vs. terfenadine or placebo 6 weeks total, 2 weeks in each treatment arm	No but patients were allowed to crossover to next treatment if current treatment was ineffective	Patient diaries, daily record cards, overall patient evaluations at the beginning and at the end of each treatment allocation	4/2 LTF /29
Ciprandi 2005 Italy	Mean 26 yrs 87% male Ethnicity NR	Desloratadine (5 mg/daily in the morning) or levocetirizine (5 mg/daily in the morning) or placebo (one tablet/daily in the morning) for 4 weeks	No other pharmacological interventions allowed	Through questions made by the investigator: nasal obstruction, sneezing, rhinorrhea, and itchy nose. Each symptom was evaluated on the following scale: 0 = absent, 1 = mild (symptom was present but was not annoying or troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep). Total symptom score (TSS) being the sum of each individual symptom was also considered.	5/NR/30

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
Berlin 2000 USA	Active treatment vs. Placebo (SE) / Difference estimate (SE) Congestion 2.223 (0.317) vs. 1.417 (0.372) / 0.806 (0.413) P = 0.09 Daytime sleepiness 2.086 (0.311) vs. 1.263 (0.342) / 0.823 (0.377) P = 0 .06 Sleep 2.215 (0.302) vs. 1.303 (0.333) / 0.912 (0.375) P = 0.04 Rhinorrhea 0.408 (0.185) vs. 0.992 (0.158) / 0.583 (0.222) P = 0.03 Congestion 1.271 (0.329) vs. 1.746 (0.198) / 0.475 (0.338) P = 0.20 Sneezing 0.871 (0.256) vs. 0.796 (0.143) / 0.075 (0.243) P = 0 .77 Ocular pruritus 0.963 (0.299) vs. 1.004 (0.260) / 0.042 (0.345) P = 0.91 Nasal pruritus 0.933 (0.301) vs. 0.933 (0.290) / 0.000 (0.356) P = 1.00
Bruttman 1989	Most results in graphs For both active treatments Conjuctival pruritus baseline 0.5 (0.7) endpoint 0.3 erythema baseline 0.4 (0.8) endpoint 0.2 Cetirizine vs. terfenadine or placebo Treatment preferences # Investigator 16* vs. 17* vs. 5 Patient 18* vs. 16* vs. 6 * vs placebo P < 0.05
Ciprandi 2005 Italy	Data reported in graphs. TSS decreased significantly both in the desloratadine group (p < 0.05) and the levocetirizine (p < 0.01), whereas placebo-treated patients showed slight increase of TSS. The intergroup analysis revealed significant differences between levocetirizine and placebo group (p < 0.001), and between desloratadine and placebo group (P < 0.05). The analysis of single symptoms showed that levocetirizine and desloratadine were more effective than placebo in relieving all symptoms (P < 0.001 and P < 0.05, respectively).

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Demoly, 2009 [pollen-induced AR] France	DB RCT Multicenter (34)	18 years or older, 2-year history or longer of AR during the natural French cypress pollen season (from January to March), clinically symptomatic with cypress pollen AR at baseline, and had a positive skin prick test result (allergen papule diameter 3 mm) to cypress pollen and/or a positive cypress pollen specific IgE radioallergosorbent test result obtained within 24 months.	Pregnancy, lactation, rhinitis medicamentosa, an upper respiratory tract or sinus infection requiring antibiotic therapy within 14 days, a viral upper respiratory tract infection within 7 days, nasal structural abnormalities significantly interfering with nasal airflow, or current evidence of any clinically significant disease or disorder that might interfere with study evaluations or affect patient safety.
Dorow 1987	DB RCT	Presence of rhinorrhea, sneening, itching nose and eyes and lacrimation	NR
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
Demoly, 2009 [pollen-induced AR] France	Mean 40 yrs 44% male Ethnicity NR	Desloratadine, 5 mg, or placebo for 15 days	Prohibited medications (eg, corticosteroids, cromolyn, antihistamines, or leukotriene inhibitors)	Patients evaluated symptoms every morning and evening and recorded the results in diaries, along with twice-daily PNIF values. The validated French-language version of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was completed by each patient at baseline and on day 14. On day 14, the investigator evaluated the global response to therapy using a 5-point scale (from 1 [complete relief] to 5 [no relief]).	100/NR/224
Dorow 1987	Mean age 42.4 yrs 63% male Ethnicity NR	Azelastine vs. placebo 1 week	NR	Patient records of symptoms, physiciansd overall assessment at endpoint	NR/NR/16
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
Demoly, 2009 [pollen-induced AR] France	Desloratadine vs. placebo Decrease in total nasal symptom score 40% vs 30%; P = 0.04 Mean individual symptom score 1.2 (47% decrease) vs. 1.6 (37% decrease) P = 0.01 Sneezing 0.59 vs. 0.44 P = 0.02 Itching 0.48 vs 0.29 P = 0.04 Rhinorrhea 0.40 vs 0.35 P = 0.58 Nasal congestion 0.33 vs 0.27 P = 0.35), RQLQ -1.4 vs. -0.09 P = 0.004 investigator evaluation of global response to therapy mean score 3.4 vs. 3.9; P = 0.004).
Dorow 1987	Azelastine vs. placebo Physician rated good or very good 7/8 vs. 0/8 P = 0.001 Symptoms moderate or severe day 1/ day 8 Sneezing 8/1 vs. 7/6 P = 0.009 Itchy nose 8/1 vs. 7/6 P = 0.009 Swelling nasal mucosa 5/1 vs. 6/5 P =0.067 Rhinorrhea 4/1 vs. 6/4 P = 0.262
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
Golden 2000 USA	Double-blinded, crossover fashion Single center	Aged 18 to 55, year round symptoms, poor sleep quality, daytime somnolence, daytime fatigue, nasal congestion, perennial allergic rhinitis with skin test positive for perennial allergens (wheal greater than 3 mm), and otherwise healthy individuals.	Seasonal allergies by skin test or history, obesity, sleep apnea, nasal polyps, asthma, deviated nasal septum, tobacco abuse, and recent upper respiratory tract infection.
Hampel 2006 USA	DB RCT, three-armed study, multicenter	12 years of age or older and had at least a 2-year history of nonrecalcitrant SAR defined by case history and positive allergen skin test.	Concurrent upper airway disease, used prohibited medications that would confound the evaluation of the study drug, or were known to be unresponsive to antihistamine therapy

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
Golden 2000 USA	NR	Azelastine nasal spray or placebo (saline nasal spray) at two sprays per nostril BID 8 weeks, crossover at 4 weeks	None allowed	Daily diary, sleep diary, questionnaires, and the Epworth Sleepiness Scale.	5/0/19
Hampel 2006 USA	Mean age 39 yrs 33.6% male 64.6% white 29.2% Hispanic 4.4% black 1.3% Asian 0.4% other races.	Olopatadine 0.6% Olopatadine 0.4% Placebo For 2 weeks	NR except as noted in exclusion	RQLQ administered to all patients at the randomization and the end of treatment visits and patient recorded diaries for symptoms	NR/NR/675

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
Golden 2000 USA	Azelastine vs. placebo (SE) Rhinitis severity score Runny nose 0.408 (0.185) vs. 0.992 (0.158) P = 0.03 Nasal congestion 1.271 (0.329) vs. 1.746 (0.198) P = 0.197 Sneezing 0.871 (0.256) vs. 0.796 (0.143) P = 0.766 Itching eyes 0.963 (0.229) vs. 1.004 (0.260) P = 0.907 Itching nose/throat 0.933 (0.301) vs. 0.933 (0.290) P = 1 Symptom Severity Questions from Daily Diary Nasal congestion 1.587 (0.368) vs. 1.555 (0.207) P = 0.932 Daytime sleepiness 1.515 ((0.281) vs. 1.578 (0.219) P = 0.837 Daytime fatigue 1.669 (0.249) vs. 1.676 (0.214) P = 0.98 Sleep problems 1.228 (0.232) vs. 1.073 (0.165) P = 0.526 Symptom Improvement With Medication Questions from Daily Diary Night time sleep quality 2.215 (0.302) vs. 1.303 (0.333) P = 0.041 Daytime sleepiness 2.086 (0.311) vs. 1.263 (0.342) P = 0.060 Nasal congestion 2.223 (0.317) vs. 1.417 (0.372) P = 0.87
Hampel 2006 USA	Olopatadine 0.6% vs. Olopatadine 0.4% vs. Placebo (SD) RQLQ Overall mean change 1,1* vs. 1.1*vs 0.8 Activities 1.3 (1.6)* vs. 1.2 (1.6) vs. 0.9(1.5) Sleep 1.3 (1.7)* vs. 1.1 (1.6) vs. 0.8 (1.6) Non–nose/eye symptoms 0.9 (1.5) vs.0.9 (1.4)* vs. 0.6 (1.3) Practical problems 1.3 (1.8)* vs. 1.4 (1.6)* vs. 0.8(1.6) Nasal symptoms 1.3 (1.6)* vs. 1.3 (1.5)* vs. 0.9 (1.4) Eye symptoms 1.3 (1.6)* vs. 1.2 (1.6)* vs. 0.8 (1.4) Emotional function 1.1 (1.6)* vs. 1.0 (1.6)* vs. 0.7 (1.4) TNSS mean % change 30.1* vs. 27.6* vs. 18.7 * vs. placebo P < 0.05

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Ho 2007 Taiwan Allergic rhinitis	Randomized trial, Center NR	Allergic rhinitis Healthy adult men and women who had a clinical history of allergic rhinitis for at least 2 years and who tested positive only for mite allergy in the multiple allergen simultaneous test.	Any chronic nasal diseases or if they had received corticosteroid nasal spray, oral antihistamine, oral decongestant, or oral corticosteroids in the past 3 months.
Holmberg 2009 France and Sweden Persistent allergic rhinitis	DB RCT 115 hospital units and private centers	PAR Aged 18–65 years, had a positive skin prick test or radioallergosorbent test of class 2 or more to house dust mite or cat dander within 24 months prior to screening, and had at least a 2-year history of moderate-to-severe nasal symptoms associated with allergen exposure.	History of allergic reactions to H1-receptor antagonists or multiple drug allergies; any clinically relevant disease or structural defect that might interfere with study evaluations; or asthma, with the exception of mild intermittent asthma; intranasal or systemic corticosteroid or an investigational drug within 30 days .

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
Ho 2007 Taiwan Allergic rhinitis	Age range 18 to 68 years 62% male Ethnicity NR	No treatment (P group), 10 mg of cetirizine once per day (C group), 20 mg of zafirlukast once per day (Z20 group), 20 mg of zafirlukast twice per day (Z40 group), a combination of 20 mg of zafirlukast and 10 mg of cetirizine once per day (Z20 C group), or a combination of 20 mg of zafirlukast twice per day and 10 mg of cetirizine once per day (Z40 C group). 1 month	NR	Patients assessed their subjective sensations of sneezing, rhinorrhea, and nasal obstruction. Symptoms were graded on a scale of 0–10, with 0 representing no perceived symptoms and 10 representing the greatest severity of symptoms imaginable, at baseline and after treatment.	NR/NR/120
Holmberg 2009 France and Sweden Persistent allergic rhinitis	Mean age 34.4 yrs 48% male Ethnicity NR	Desloratadine 5 mg/day (n = 293) or placebo/ day (n = 291) for 28 days.	Concomitant medications that would interfere with the evaluations were not permitted; could not have received specific immunotherapy within 4 months.	Mean change from baseline to the end of the study in the nasal congestion score recorded twice daily, the 28-item RQLQ (14) at baseline, on days 7 and 28.	Per article more than 80% completed / LTF NR / 584

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
Ho 2007 Taiwan Allergic rhinitis	Data reported in graphs Total symptom score improved after treatment in the treated group (p = 0.05;). High-dose anti-LT alone (Z40) and the combination of anti-LT, including low- and high-dose, and antihistamine (Z20 C and Z40 C) caused better results than the low-dose anti-LT (Z20) or antihistamine (C) alone. In the C group, the symptoms of sneezing and rhinorrhea improved significantly , but nasal obstruction did not improve. In the Z20 group, rhinorrhea improved, but sneezing and nasal obstruction did not . All allergic symptoms, including sneezing, rhinorrhea, and nasal obstruction, were significantly reduced after Z40, Z20 C or Z40 C treatment; however, the treatment effect was similar in Z40, Z20 C, and Z40 C groups
Holmberg 2009 France and Sweden Persistent allergic rhinitis	Desloratadine vs. placebo RQLQ scores (SD) at day 28 Activity limitation 2.8 (1.5) vs. 3.2 (1.6) P = 0.005 Sleep problems 1.7 (1.4) vs.1.9 1.5) P = 0.018 General problems 1.7 (1.3) vs. 1.9 (1.3) P = 0.012 Practical problems 2.5 (1.6) vs. 2.9 (1.6) P = 0.004 Nasal symptoms 2.4 (1.3) vs. 2.7 (1.4) P = 0.0002 Ocular symptoms 1.4 (1.4) vs. 1.5 (1.5) P = 0.35 (ns) Emotional function 1.5 (1.2) vs.1.8 (1.4) P = 0.007 Total score 1.9 (1.1) vs. 2.2 (1.2) P = 0.008 Desloratadine vs. placebo mean change from baseline in a.m./p.m. total nasal symptom score and rhinorrhea score (both P $\leq$ 0.01). Most data reported in graphs.

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Kim 2006 Multinational	Randomized, double-blind, placebo-controlled trial, multicenter (67)	12 years or older with a history of PAR for at least 2 years. Patients were required to have a TSS of 9 or greater, a TNSS of 5 or greater, and a TNNSS of 4 or greater at the initial screening visit and a positive skin prick response to an appropriate perennial allergen (eg, dust mites or animal dander) within 12 months of the study	Structural abnormalities that interfered with nasal airflow, a current diagnosis or a history of acute or chronic sinusitis, chronic purulent postnasal drip, rhinitis medicamentosa, asthma that required regular use of systemic or inhaled corticosteroids, or a skin test that demonstrated mold as the only qualifying perennial allergen. Additional exclusion criteria included the use of any investigational drugs within 30 days of screening and dependence on nasal topical antihistamines, nasal corticosteroids, or nasal, oral, or ocular decongestants. Patients receiving immunotherapy were excluded unless they had been taking medication on a regular maintenance schedule before screening and could maintain this schedule for the duration of the study.
NCT00521131 2007	Double-blind, placebo-controlled, randomized, multicenetr	≥ 12 years of age with perennial allergic rhinitis to house dust mites for > 2 years, a positive skin test or positive Radio-Allergo-Sorbent-Test for house dust mites, and having a mean Total 4 Symptoms Score ≥ 5 (T4SS; sum of the scores of the severity of sneezing, rhinorrhea, nasal pruritis and ocular prurtis) over the selection period and a T4SS ≥ 5 on the day before randomization.	Pregnant, potentially pregnant or breast feeding

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
Kim 2006 Multinational	Mean age 35 yrs 44% male 83% white	Desloratadine, 5 mg, vs. Placebo 4 weeks	See exclusion criteria and nasal or ophthalmic cromolyn or nedocromil, corticosteroids (other than low- or moderate-potency dermatologic preparations), H1-antihistamines other than desloratadine, leukotriene modifiers, intranasal atropine or ipratropium bromide, ocular or intranasal saline, systemic antibiotics, and nasal, oral, or ocular decongestants were prohibited	The severity of PAR symptoms, during the preceding 12 hours (reflective) and at the present time (instantaneous), was graded according to a 4-point scale (0 none present; to 3 - signs or symptoms difficult to tolerate and may interfere with daily activities or sleeping [severe]). Scores for individual symptoms combined to obtain the TSS (rhinorrhea, nasal congestion/ itching, sneezing, itching/burning eyes, tearing/watering eyes, and itching of the ears/palate), the TNSS (rhinorrhea, nasal congestion/itching, sneezing), and the TNNSS (itching/ burning eyes, tearing/watering eyes, and itching of the ears/ palate). Patients and investigators jointly evaluated the overall severity of PAR using the same 4-point scale at visits	107/NR/1179
NCT00521131 2007	Mean age 35 yrs 37% male 94% white 2% Asian/Pacific Islander 4% black	Levocetirizine dihdrochloride vs. placebo for 30 days	NR	Number of comfortable days over a 30-day treatment period	94/NR/443

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
Kim 2006 Multinational	Desloratadine, 5 mg, vs. Placebo mean reductions from baseline TSS 3.9 (mean change, 26.6%) vs. 3.2 (mean change, 22.3%), P = 0.001 TNSS 2.1 (mean change, 23.7%) vs. 1.8 (mean change, 19.8%) P = 0.004 TNNSS 1.8 (mean change, 30.6%) vs.1.5 (mean change, 25.9%) P < 0.001) Overall condition of PAR 0.65 [mean change, 24.2%]) vs. 0.53 [mean change, 19.5%]; P = 0.01.
NCT00521131 2007	Levocetirizine dihdrochloride vs. placebo f Total treatment period mean (SD) 9.36 (9.86) vs. 12.81 (11.08) Adjusted mean (SE) 9.38 (0.69) vs. 12.78 (0.70) Difference in adjusted mean (95% CI), LCTZ 5 mg minus PBO 3.40 (1.48, 5.32) P = 0.002

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
Pasquali 2006 Italy Persistent allergic rhinitis and asthma	RCT, single center	PAR Adult outpatients (>18 years) of both genders; persistent allergic rhinoconjunctivitis with a history of mild intermittent asthma from at least 2 years or actual asthma (last month). The diagnosis of persistent rhinitis was made on a clinical basis, according to the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria [2], whereas asthma was diagnosed and graded according to GINA guidelines [16]. A positive (weal diameter >3 mm) skin prick test (SPT) and/or CAP-RAST (class II or higher) for at least house dust mites and/or parietaria .	Anatomical abnormalities of the nose (turbinate hyperthrophy, septal deviation, polyps), pregnancy, persistent asthma, chronic treatment with systemic steroids, malignancies, systemic immunological disorders and ongoing specific immunptherapy.
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 duration of the study; desensitization treatment within 24 hours before a study visit was prohibited. Pregnant or nursing women also 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
Pasquali 2006 Italy Persistent allergic rhinitis and asthma	Mean age 35.1 yrs 40% male Ethnicity NR	Levocetirizine 5mg versus placebo for 8 weeks	Cromolyn and salbutamol were permitted on demand	Patient diary card for symptoms. All symptoms were graded using a score from 0 (absent at all) to 3 (very troublesome). Five symptoms were considered for rhinoconjunctivitis (so-called T5SS): rhinorrhoea, itching, sneezing, nasal congestion and ocular itching. Also, five lower airways symptoms (cough, wheezing, dyspnoea, chest tightness, night awakenings); how many times he/she used nasal and ocular cromones and/or salbutamol. A weekly symptom score (possible maximum value 105) was calculated for statistical analysis were recorded throughout the 9 weeks. QoL (generic and specific) and nasal inflammatory cells and mediators were assessed at the end of run-in (visit 2), after 2 (visit 3), 4 (visit 4) and 8 weeks (visit 5) of treatment.	10/0/NR They start with 50, 10 drop out and they do not report the # 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
Pasquali 2006 Italy Persistent allergic rhinitis and asthma	Data reported primarily in graphs T5SS - difference between groups was achieved at week 3 (P = 0.035) and maintained to the end In the asthmatic patients, the average number of doses of salbutamol was: in the active group 4.75/week at baseline and 2.35/week in the 2 months of treatment; placebo 5.2/week at baseline and 5.0/week at baseline , with a significant difference between groups.
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 3. Perennial allergic rhinitis trials in adults

Author Year Country	Study Design Setting	Population Eligibility criteria	Exclusion criteria
UCB 2008 A study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of perennial allergic rhinitis	Randomised, investigator blinded, active-control, parallel-group study Multicenter (2)	Male and female, aged 18 to 60 years and were clinically diagnosed with PAR.	NR

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
UCB 2008 A study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of perennial allergic rhinitis	Mean age 37 yrs 39% male 100% Asian / Mongolian	5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine	NR	Change of investigator assessed T5SS from baseline to end of treatment at 14 days	5/NR/71

Evidence Table 3. Perennial allergic rhinitis trials in adults

Author Year Country	Results
UCB 2008 A study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of perennial allergic rhinitis	Least Square mean changes from baseline of T5SS was –4.54 for LCTZ group and –3.83 for LRTD group, P = 0.3552

Evidence Table 4. Quality assessment of perennial 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?
Bachert 2004	Unclear	Unclear	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Unclear, reported as double-blind
Berlin 2000	No	NR	NR	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described
Bruttman 1989	NR	NR	NR	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Yes
Ciprandi 2005	NR	NR	Incomplete data provided	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described
Demoly 2009 Pollen-induced AR	NR	NR	No More women in placebo group, p=.04	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described

Evidence Table 4. Quality assessment of perennial 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	Comment
Bachert 2004	Yes, No, NR, NR	No/No	Yes	No	UCB	Fair	
Berlin 2000	Attrition: 6/44 (13.6%) did not complete Crossovers, adherence and contamination: NR	Yes 1/20 (5%) vs. 5/24 (21%)	No only completers included in ITT (13.6% excluded)	NR	General Clinical Research Center, Peen State, supported by NIH	Poor	Randomization and allocation not adequate; data on baseline charactoristics not adequately described; high and differential loss to follow-up; no ITT.
Bruttman 1989	Attrition reported, along with adherence, crossover and contamination	Difficult to determine. 2/33 reported lost to follow-up but only 25/33 in full analysis	No 25/33 (76%) included in ITT	Yes	Not reported	Poor	
Ciprandi 2005	NR	NR	NR	NR	NR	Poor	Small n, insufficient information reported
Demoly 2009 Pollen-induced AR	Attrition and adherence reported	Yes 47% of placebo and 39% of desloratadine did not complete	No 224/233 (96%) in ITT	Yes	Schering-Plough	Fair	

Evidence Table 4. Quality assessment of perennial 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?
Dorow 1993	NR	NR	No weight and gender differences	Not adequately. Inclusion criteria only met by 8/16	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Yes
Frolund 1990	Yes, computer generated code	NR	Yes	Yes	NR	NR, same assessor each time	Yes, identical capsules all twice daily
Golden 2000	NR	NR	Yes	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described
Hampel 2006	NR	NR	No significant gender differences	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described

Evidence Table 4. Quality assessment of perennial 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	Comment
Dorow 1993	Report says all completed but only 8/16 met inclusion criteria	No	No Report says all completed but only 8/16 met inclusion criteria	No	ASTA Medica AG	Poor	Small N. Inclusion criteria only met by 8/16.
Frolund 1990	NR	Yes, 16%	Appears yes for AEs	NR	Manufacturer funded	Fair	Quality rating-patient diary responses reported in figures without individual values
Golden 2000	Attrition: 5/24 (21%) Others, no	No/No	Yes	No	NR	Fair	
Hampel 2006	NR	NR	NR 675 in ITT but no data on how many were randomized. ITT = in tx with > 1 visit	NR	Alcon Research, Ltd.	Poor	Insufficient information reported

Evidence Table 4. Quality assessment of perennial 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?
Ho 2007	Methods not reported	NR	Yes	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described
Holmberg 2009 Persistent	NR	NR	Yes	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Reported as "double-blind" but not described
Pasquali 2006 Persistent	Yes, computer generated code	NR	Unclear Minimal information provided on clinical charactoristic	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Yes
Kim 2006	Methods not reported	NR	Yes	Yes	Reported as "double-blind" but not described	Reported as "double-blind" but not described	Yes, identical capsules
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

Evidence Table 4. Quality assessment of perennial 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	Comment
Ho 2007	NR	Unclear	NR	NR	Grants from the National Science Counsil and Veterans General	Fair	
Holmberg 2009 Persistent	Report states > 80% completed. No completion data provided. Adherence reported.	Report states > 80% completed with similar rates of withdrawal between groups. Data not provided.	Yes	No	Schering-Plough	Fair	
Pasquali 2006 Persistent	Attrition reported Crossovers, adherence and contamination: NR	Yes - high 10/50 (20%) dropped out, 5 from each group	NR	No	Partially supported by: ARMIA (Associazione Ricerca Malattie	Fair	
Kim 2006	Attrition yes, others no.	No (91% completed)	NR	NR	Schering-Plough	Fair	
Simons 2003	Attrition yes, others no.	No	Unable to determine, number analyzed not reported	NR	Schering-Plough	Fair	

Evidence Table 4. Quality assessment of perennial 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?
UCB, NCT00521131, A double blind…	Method not described	Not described	Yes (demographics only reported)	Yes	Unclear, described as double blind	Unclear, described as double blind	Unclear, described as double blind
UCB NCT00524836, A study evaluating the efficacy…	Method not described	Not described	NR	Yes	Unclear, described as investigator blinded	Unclear, described as investigator blinded	Unclear, described as investigator blinded

Evidence Table 4. Quality assessment of perennial 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	Comment
UCB, NCT00521131, A double blind…	Attrition reported, none of others reported	Yes, 23% placebo and 15% treatment group withdrew	No, 10 patients excluded from analysis	No	UCB	Poor	
UCB NCT00524836, A study evaluating the efficacy…	Attrition reported, none of others reported	No	Unclear, but low attrition	No	UCB	Fair	

Evidence Table 5. 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				
Garg 2007 India	Observational - single center	CIU Those showing complete symptomatic control of CIU at 6 weeks with cetirizine were shifted to an equivalent dose of 5 mg of levocetirizine and were assessed weekly	NA	Age range 15–65 years 60% male Ethnicity NR
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 5. 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				
Garg 2007 India	Cetirizine 10 mg then levocetirizine 5 mg Studied sequentially for 6 weeks each	NR	Weekly assessment of wheal, flare and itch responses on a visual analog scale of 0–3 (0 -asymptomatic, 1 -mild, 2 - moderate, 3 - maximum severity)	20/NR/30
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 5. Urticaria trials in adults

Author Year Country Quality score	Results
Head-to-head trials	
Garg 2007 India	Cetirizine vs. levocetirizine Wheal response 30 vs. 28 Flare response 30 vs. 30 Itch response 30 vs. 9
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 5. Urticaria trials in adults

Author Year Country Quality score	Study design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Thomas 1998 India	Randomized investigator-blinded parallel group, multicenter	12 to 60 years suffering from urticaria for at least 6 weeks	History of asthma, other systemic conditions that could interfere with the study, multiple drug allergies, known non-response to antihistamines, patients suffering from pressure urticaria or cold urticaria and women who were pregnant, nursing or using birth control pills; antihistamines for 72 hours, systemic corticosteroids for 1 month, topical steroids for 2 weeks, cromolyn for 2 weeks and decongestants for one day preceding the trial.	NR, article states, "The two groups were similar in sex, age and weight"

Evidence Table 5. 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
Thomas 1998 India	Loratadine vs. cetirizine	NR but see excusions	Physicians and portents evaluated the number of lesions and episodes, the average size and duration of lesions, and the degree of pruritus on a 4 point scale at baseline and days 3, 7, 14 and 27	8/8/202

Evidence Table 5. Urticaria trials in adults

Author Year Country Quality score	Results
Thomas 1998 India	Data reported in graphs Loratadine vs. cetirizine The number, size and the duration of lesions P < 0.05 Fall in the mean score of pruritus P < 0.05 All favored loratadine

Evidence Table 5. Urticaria trials in adults

Author Year Country Quality score	Study design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Placebo-controlled trials				
Grob 2008 France	DB, RCT, multicentre (40)	CIU 18 years of age, history of CIU (i.e. pruritus and weals lasting 6 weeks; in good general health. CIU symptoms present for 3 weeks, with weals present for 3 days a week and a flare-up before visit 1 (previously untreated patients) or after discontinuation of prior treatment and completion of a drug-specific washout eriod, pruritus score of 2 (at least moderate pruritus), a weal score of 1 (at least 1–6 weals) and a global CIU severity score of 2 (at least moderate severity) at screening and baseline, also required to show an am/pm reflective pruritus score of 14 for the three consecutive days prior to baseline and the morning of day 1.	Pregnant or nursing, or expected to become pregnant during the study; had asthma requiring chronic inhaled or systemic corticosteroids; had been injected with corticosteroids within 90 days; had been hospitalized for CIU for 3 months ; had antihistamineresistant CIU; or had skin reactions due to drug- or foodrelated allergies; hypersensitivity to desloratadine or any of its excipients, clinically significant conditions that might interfere with the evaluation of CIU or compromise safety and the presence of affective or intellectual disorders that might invalidate informed consent or impede cooperation with study procedures. Treatment with other experimental medications was forbidden for 30 days or for 90 days in the case of experimental antibodies for asthma or allergic rhinitis.	mean age 41 yrs 39% male Ethnicity NR
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 5. 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				
Grob 2008 France	Desloratadine 5 mg vs. placebo 6 weeks	see exclusions	DLQI and Total VQ-Dermato scores (range from 0 (least serious effect) to 112 (worst effect)) at visit 2 (baseline) and visit 5 (day 42) Daily patient diary of sleep disruption and disruption of daily activities	57/1/137
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 5. Urticaria trials in adults

Author Year Country Quality score	Results
Placebo-controlled trials	
Grob 2008 France	Desloratadine vs. placebo Change from baseline DLQI (SD) –6(6.2) vs. –2.2 (5.1) P < 0.001 VQ-Dermato (SD) –15.0 (17.7) vs. –8.0 (18.8) P = 0.035 **VQ-Dermato domain scores at day 42** Daily activities 18.1 vs. 32.6 P = 0.001 Mood 7.5 vs. 14.7 P = 0.027 Social life 10 vs. 21 P = 0.005 Physical pain 42.3 vs. 58.2 P = 0.006 Self-image 21.5 vs. 30 P = NS Leisure activities 19.7 vs. 26.2 P = NS Limitations due to treatment 3.1 vs. 12.9 P = NS
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 5. Urticaria trials in adults

Author Year Country Quality score	Study design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Kapp 2006 Germany and Switzerland	randomized, double-blind, placebo-controlled, parallel, multicenter study (19)	CIU CIU, i.e. episodes of hives of characteristic wheal and flare appearance, occurring regularly, at least three times a week for a period of at least 6 weeks during the previous 3 months, without an identifiable cause.	other forms of urticaria, such as physical, drug-induced, acute, or cholinergic urticari and any systemic disease or dermatologic disease that could have interfered with the evaluation of the symptoms	Mean age 42 yrs 41% male Ethnicity NR

Evidence Table 5. 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
Kapp 2006 Germany and Switzerland	Levocetirizine, 5 mg, vs. placebo	No relief or rescue medication was provided; an analysis of the concomitant medications linked to urticaria reported was performed	Patients used daily record cards to record their symptoms once a day in the evening . A four-point scale from absent (0) to severe (3) was used to evaluate pruritus severity over the last 24 h. The number of wheals was reported using a 0–3 scale (0, no wheals; 1, 1–6 wheals; 2, 7–12 wheals; 3, 12 wheals) and their size was evaluated using a similar scale. The duration of pruritus was evaluated daily by the patients using a four-point scale (0, no pruritus; 1, < 1 h; 2, 1–6 h; 3, 6 h). At each visit, the investigator evaluated the same parameters using the same scales, and also indicated the presence or absence of dermographism (urticaria factitia), angioedema, and pressureinduced urticaria. End-of-treatment visit, a global evaluation scale (7 points) was completed by answering the question: “Overall, has there been a change in your urticaria since the start of the study medication?”	42 (33 placebo (38.8%) and 9 levocetirizine 5 mg group (11.1%)/0/166

Evidence Table 5. Urticaria trials in adults

Author Year Country Quality score	Results
Kapp 2006 Germany and Switzerland	Levocetirizine vs.placebo at 4 weeks Pruritus severity score (SE) 1.56 (0.09) vs. 0.94 (0.09) P< 0.001 Duration of pruritus (SE) 1.57 (0.09) vs. 0.98 (0.09) P < 0.001 Number of wheals (SE)1.51 (0.10) vs. 1.04 (0.10) P = 0.001 Size of wheals (SE) 1.35 (0.09) vs. 0.96 (0.09) P = 0.001 Change in DLQI 7.3 vs. 2.4 absenteeism 0.8 working days lost per month vs.1.8 working days lost per month overall loss of productivity -0.5 days vs, + 1.5 days per month

Evidence Table 5. 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 5. 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 5. 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 5. Urticaria trials in adults

Author Year Country Quality score	Study design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Nettis 2006 Italy	DB RCT Single center	Patients with delayed pressure urticaria (DPU)	Concomitant illness (e.g. malignancies or hepatic, psychiatric, endocrine or other major systemic diseases), pregnancy, pregnancy potential or currently breastfeeding.	Mean age 35 58% male Ethnicity NR
Nettis 2006 Italy	DB RCT Single center	Diagnosis of chronic idiopathic urticaria	Physical urticaria, or urticaria caused by medications, insect bites, food or other known causes, as well as a history of atopic diseases. Patients with significant concomitant illness (e.g. malignancies or hepatic, psychiatric, endocrine or other major systemic diseases)	39 years old 37% male Ethnicity NR

Evidence Table 5. 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
Nettis 2006 Italy	Oral desloratadine 5 mg plus oral placebo vs. oral desloratadine 5 mg plus montelukast 10 mg vs. oral placebo alone.	Medications that could interfere with the clinical evaluations and systemic or topical medication for urticaria, other than those specified in the study treatment, were not allowed during the trial	The difference in weal size (pressure challenge lesion area) between baseline and the end of the 2-week treatment, self-evaluation of skin lesion scores regarding erythema, oedema and pruritus, using a four-point scale (0, none - 3,severe), and by the decrease of number of separate urticarial episodes (0, no episodes - 3, more than three episodes).	2/0/34
Nettis 2006 Italy	Oral levocetirizine 5 mg, vs. oral placebo 6 weeks	"No medications that could interfere with the clinical evaluations were allowed during the trial."	Patients recorded their symptoms in a daily diary, including pruritus, size of weals, number of weals, number of separate urticarial episodes.	6/0/100

Evidence Table 5. Urticaria trials in adults

Author Year Country Quality score	Results
Nettis 2006 Italy	desloratadine plus montelukast vs. desloratadine Mean score decrease TSS value 97.2% vs. 41.1% Pruritus score 70.8% vs. 53.9% Erythema score 66.7% vs. 34.8% Oedema score 73.9% vs. 36.4% Number of episodes score 61.1% vs. 42.2% desloratadine plus montelukast vs. desloratadine vs. placebo (baseline/endpoint) mean (SD) Pressure challenge diameter (mm) 13.7 (1.6) / 0.8 (1.9) vs. 13.4(1.5) / 7.0(4.7) vs. 12.8(1.9) / 11.8 (2.2) Pruritus score 2.4(0.8) / 0.7(0.5) vs. 2.6(0.7) / 1.2(0.6) vs. 2.3(0.9) / 2.5(0.8) Erythema score 2.4(0.7) / 0.8 (0.8) vs. 2.3(0.6) / 1.5 (0.7) vs. 2.4(0.8) / 2.4(0.8) Oedema score 2.3(0.8) / 0.6(0.8) vs. 2.2(0.9) / 1.4(0.8) vs. 2.4 (0.8) / 2.4(0.7) Number of separate episodes score 1.8(0.8) / 0.7(0.5) vs. 1.9(0.8) / 1.1(0.5) vs. 1.7(0.9) / 1.5(0.7)
Nettis 2006 Italy	Levocetirizine 5 vs. placebo Mean TSS value decrease 81% vs. 1% Total disappearance of symptoms 27 (53%) vs. 0 The rest of the outcomes only report active results and not placebo

Evidence Table 5. Urticaria trials in adults

Author Year Country Quality score	Study design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Ortonne 2007 France	DB RCT Multicenter (40)	Moderate to severe chronic idiopathic urticaria patients; active for 3 weeks or longer; with wheals for at least 3 days a week and a global CIU severity score of 2 or more; greater than 18 years old.	Hospitalized for CIU aggravation in the 3 months or if they had urticaria due to physical or other known causes, skin or food allergies that manifested as skin reactions, prior to antihistamine treatment, a history of hypersensitivity to desloratadine or any of its excipients, or asthma requiring long-term treatment with inhaled or systemic corticosteroids; investigational medications in 30 days prior or investigational antibodies for asthma or allergic rhinitis in the 90 days; individuals with clinically significant psychiatric, cardiovascular, or other pathologic conditions that could interfere with the study evaluation, compromise patient safety, or patient's consent to partake; history of poor motivation or non-compliance with medications or treatment protocols.	Mean 41 years 39% male Ethnicity NR
Potter 2009 Multinatiional	DB RCT Multicenter	Male and female out-patients aged 18 years and over, with a clinical history of CIU (i.e. episodes of hives of characteristic wheal and flare appearance, occurring regularly, at least three times a week) for a period of at least 6 weeks during the last 3 months without an identifiable cause	Physical urticaria, drug-induced urticaria, urticarial vasculitis, senile pruritus or hereditary angioedema, any dermatological or any other clinically significant disease, received systemic and topical corticosteroids within 4 weeks, desloratadine, loratadine, levocetirizine or cetirizine,within 10 days, astemizole within 12 weeks, ketotifen within 2 weeks, and leukotriene antagonists within 3 days, received CNS acting agents (including tranquilizers, antidepressants, sedatives, hypnotics or antiepileptics) at any time and pregnant or breastfeeding.	43.1 years 33.4% male 81.6 % Caucasian 13.7% Asian/Pacific Islander 1.5% Black 3.3% other

Evidence Table 5. 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
Ortonne 2007 France	desloratadine 5mg daily vs. placebo 6 weeks	NR except the excluded drugs	pruritus severity, number of wheals, and the size of the largest wheal assessed 2x a day and overall therapeutic response at the end of the 6-weeks	52/3/137
Potter 2009 Multinatiional	Levocetirizine 5 mg vs.desloratadine 5 mg	Yes- concomitant medication use was recorded	Mean pruritus severity score after 1 week of treatment and mean pruritus severity score over 4 weeks and pruritus duration score, number and size of wheals, mean CIU composite score (sum of the scores for pruritus severity and numbers of wheals), quality of life, and the patient s and investigator s global satisfaction with treatment,	54/6/886

Evidence Table 5. Urticaria trials in adults

Author Year Country Quality score	Results
Ortonne 2007 France	Desloratadine vs placebo Complete, marked, or moderate therapeutic response 68.8% vs. 36.8% P < 0.001 Reduction of pruritus scores (SD) -1.43(0.93) vs. -0.86(1.14) P = 0.004
Potter 2009 Multinatiional	Levocetirizine vs.desloratadine Pruritus severity score First treatment week 1.02 (0.04) vs. 1.18 (0.04) P < 0.001 Entire treatment period 0.86 (0.04) 434 0.99 (0.04) P = 0.004 Pruritus duration score First treatment week 1.08 (0.04) vs.1.24 (0.04) P = 0.002 Entire treatment period 0.93 (0.04) vs. 1.05 (0.04) P = 0.009 Number of wheals score First treatment week 0.96 (0.04) 434 1.05 (0.04) P = 0.054 Entire treatment period 0.85 (0.04) vs. 0.89 (0.04) P = 0.353 Size of wheals score First treatment week 1.01 (0.04) 434 1.12 (0.04) P = 0.025 Entire treatment period 0.89 (0.04) vs. 0.97 (0.04) P = 0.085 CIU composite score* First treatment week 1.98 (0.08) vs. 2.23 (0.08) P = 0.005 Entire treatment period 1.71 (0.07) vs. 1.88 (0.07) P = 0.041

Evidence Table 5. Urticaria trials in adults

Author Year Country Quality score	Study design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ ethnicity
Active-control 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 5. 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-control 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 5. Urticaria trials in adults

Author Year Country Quality score	Results
Active-control 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 6. 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							
Garg 2007	NA	NA	Yes (because crossover, so same patients)	Yes	Open label	Open label	Open label
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"
Thomas 1998	Method not reported	NR	Yes, though no data presented in a table	Yes	NR; study reported as 'double blind'	NR; study reported as 'double blind'	NR; study reported as 'double blind'
Placebo-controlled trials							
Kapp 2006	Method not reported	NR	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	NR; study reported as "double blind"
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"
Nettis 2006 (Levocetrizine)	Method not reported	Method not reported	No	Yes (but not adequately)	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Nettis 2006 (Desloratadine)	Method not reported	Method not reported	No	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes

Evidence Table 6. 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	Quality rating
Head-to-head trials						
Garg 2007	Attrition reported, but reasons NR; cross-overs, adherence, and contamination NR	Yes 20/50 (40%) dropped	NR	NR	NR	Fair
Guerra 1994	NR	Yes	Yes	NR	NR	Fair
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	Fair
Thomas 1998	Attrition reported, but reasons NR; cross-overs, adherence, and contamination NR	No; 8/210 (4%) dropped	NR	NR	NR	Fair
Placebo-controlled trials						
Kapp 2006	Attrition reported, but reasons NR; cross-overs, adherence, and contamination NR	74.7% completed	Yes	NR	UCB (Farchim, Bulle, Switzerland)	Fair
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	Fair
Nettis 2006 (Levocetrizine)	Attrition 6/106; cross-overs, adherence, and contamination NR	No Loss twice as high in placebo but small N	No - excluded 6/106 (6%)	No	NR	Fair
Nettis 2006 (Desloratadine)	Attrition 2/36; cross-overs, adherence, and contamination NR	No	No - excluded 2/36 (6%)	No	NR	Fair

Evidence Table 6. 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?**
Ortonne 2007	Yes	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Potter 2009	Yes	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"	Yes
Grob 2008	Yes	Yes	Yes	Yes	NR; study reported as "double blind"	NR; study reported as "double blind"	Yes
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
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"

Evidence Table 6. 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	Quality rating
Ortonne 2007	Attrition 57/142; cross-overs, adherence, and contamination NR	Yes 16/65 (25%) of drug discontinued: 36/77 (47%) of placebo discontinued	No - excluded 5/142 (3.5%)	Yes	Schering-Plough, Levallois Perret, France	Fair
Potter 2009	NR	NR	No Incomplete report of data. Not clear if all randomized were in ITT	NR	UCB Farchim Chemin de Croix blanche, Bulle, Switzerland.	Fair
Grob 2008	Attrition reported, but reasons NR; cross-overs, adherence, and contamination NR	No; 5/77 (6.5%) dropped from placebo group	Yes	Yes; 3 excluded because they lacked baseline data	Schering-Plough Research Group	Fair
Active-controlled trials						
Breneman 1996	NR	No, 5%	Yes	NR, NR	NR	Fair
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	Poor; very high attrition for unclear reasons; patients 'selected' into study
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	Poor; unclear if randomized, no information on how groups assigned; no wash-out between cross-over; attrition 19/30
Kontou-Fili 1990	Attrition 1/11; others NR	No, 1/11	No, attrition=1, crossovers NR	NR	NR	Poor: baseline comparability NR; attrition 1/11

Evidence Table 6. 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?**
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 6. 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	Quality rating
Monroe 2003	Attrition and adherence yes; others NR	No (3/226)	Yes	NR	Schering-Plough Research Group	Good
Sharpe 1993	Attrition 2/21; others NR	No, 2/21	No, attrition=2	NR	NR	Poor: baseline comparability NR; attrition2/21
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	Poor; treatment with placebo was single-blind, no baseline characteristics reported, randomization and allocation concealment methods NR
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	Poor: high attrition (15%), no ITT, baseline characteristics not reported by group (unable to determine if groups by order of administration were similar)

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility criteria
Active-control 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.
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.

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Exclusion criteria	Allowed other medications/ interventions	Age Gender Ethnicity
Active-control trials			
Cetirizine			
Tinkleman 1996 USA (Fair)	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	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
Loratadine			
Boner 1989 Italy (Fair)	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	NR	Mean age: 7.7y Range: 4-12 y 65% Male Ethnicity: NR Mean weight: 28.6 kg Mean height: 123.7 cm

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Interventions	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled
Active-control trials			
Cetirizine			
Tinkleman 1996 USA (Fair)	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)	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
Loratadine			
Boner 1989 Italy (Fair)	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	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

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Number withdrawn/ lost to follow-up/ analyzed	Results
Active-control trials		
Cetirizine		
Tinkleman 1996 USA (Fair)	4/ 1/ 186	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)	4/ NR/unclear	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 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility 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).
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.

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Exclusion criteria	Allowed other medications/ interventions	Age Gender Ethnicity
Jordana 1996 Canada (Fair)	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	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
Placebo-controlled trials			
Cetirizine			
Allegra et al 1993 Europe (Fair)	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)	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

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Interventions	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled
Jordana 1996 Canada (Fair)	L: Loratadine 10 mg syrup qam + placebo spray F: Fluticasone propionate 200 micrograms aqueous spray qam + placebo tablet 4-week treatment period	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
Placebo-controlled trials			
Cetirizine			
Allegra et al 1993 Europe (Fair)	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	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

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Number withdrawn/ lost to follow-up/ analyzed	Results
Jordana 1996 Canada (Fair)	12/unclear/240; 2 withdrawn prior to randomization; 12 pts were discontinued from the study for AEs, and 5 for ineffective treatment	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)	0/ 0/ 107	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 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility 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.
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.
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.

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Exclusion criteria	Allowed other medications/ interventions	Age Gender Ethnicity
Ciprandi et al 1997a Ciprandi 1997b (cough) Italy (Fair)	History of asthma or previous documented intolerance to the studied drug; any other ocular or nasal disease	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
Masi 1993 Italy (Fair)	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	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
Pearlman et al 1997, Winder et al 1996 (safety) US (Fair)	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.	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

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Interventions	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled
Ciprandi et al 1997a Ciprandi 1997b (cough) Italy (Fair)	C: Cetirizine 0.15 mg/kg qam P: Placebo qam	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
Masi 1993 Italy (Fair)	C: Cetirizine 5 mg bid P: Placebo 2 week treatment period	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
Pearlman et al 1997, Winder et al 1996 (safety) US (Fair)	C1: Cetirizine 5 mg qd C2: Cetirizine 10 mg qd P: Placebo qd	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

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Number withdrawn/ lost to follow-up/ analyzed	Results
Ciprandi et al 1997a Ciprandi 1997b (cough) Italy (Fair)	0/0/20	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)	10/ 2/ unclear	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
Pearlman et al 1997, Winder et al 1996 (safety) US (Fair)	For efficacy: 4/0/205 For safety: 4/16/189 for ECG analysis: NR/88/121	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)

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility criteria
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.

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Exclusion criteria	Allowed other medications/ interventions	Age Gender Ethnicity
Fexofenadine			
Wahn et al 2003 15 countries: Argentina, Austria, Chile, Finland, France, Germany, Israel, Italy, Poland, Portugal, South Africa, Spain, Uruguay, US (Fair)	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) .	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

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Interventions	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled
Fexofenadine			
Wahn et al 2003 15 countries: Argentina, Austria, Chile, Finland, France, Germany, Israel, Italy, Poland, Portugal, South Africa, Spain, Uruguay, US (Fair)	F: Fexofenadine 30 mg bid P: Placebo bid 2-week treatment period	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

Evidence Table 7. Seasonal allergic rhinitis trials in children

Author Year Country (Quality score)	Number withdrawn/ lost to follow-up/ analyzed	Results
Fexofenadine		
Wahn et al 2003 15 countries: Argentina, Austria, Chile, Finland, France, Germany, Israel, Italy, Poland, Portugal, South Africa, Spain, Uruguay, US (Fair)	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	Mean change from baseline on pm-reflective TSS, F vs P (4-point scale): -1.94 vs -1.21 ($p \leq 0.0001$) 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 8. 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?**
Allegra 1993	Yes, computer-generated list	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Bender 2003 US	Method not reported	Method not reported	NR	Yes	NR; "double blind"	NR; "double blind"
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
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
Jordana 1996	Method not reported	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"

Evidence Table 8. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Allegra 1993	Yes	Attrition reported (none). Crossovers, adherence and contamination NR.	No (no attrition)	Yes, assuming no cross-overs	None
Bender 2003 US	Yes (double-dummy, placebo)	NR	NR	NR	NR
Boner 1989 Italy	Parent not masked; unclear if child aware	Attrition reported (4/40); adherence measured but results NR	10% attrition	No, 36/40 analyzed; no reporting of cross-overs	No
Ciprandi 1997a Ciprandi 1997b Italy	Yes; described as 'double blind' but unclear who was blinded	Attrition yes, others no	No	Yes	No
Jordana 1996	Yes	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

Evidence Table 8. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	Funding	Quality rating
Allegra 1993	NR: Affiliation of last author is UCB Pharma Secotor R & D, B-1420 Braine-l'Alleud, Belgium	Fair
Bender 2003 US	GlaxoSmithKline	Poor: can't determine if groups were similar at baseline and number analyzed not specified
Boner 1989 Italy	NR	Fair
Ciprandi 1997a Ciprandi 1997b Italy	NR	Fair
Jordana 1996	Glaxo Canada Inc.	Fair

Evidence Table 8. 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?**
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"
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
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"
Tinkelman 1996	Method not reported	Yes (drug dispensed by nurse independent of investigator)	Yes	Yes	NR	NR
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

Evidence Table 8. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
Masi 1993	Yes	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
Pearlman 1997, Winder 1996 (safety) US	Study described as 'double blind' but unclear who was blinded	Attrition reported, adherence and contamination no	No	No (205/209 analyzed)	2 patients removed for poor compliance and 1 for protocol violation
Segal 2003	Yes	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.
Tinkelman 1996	No	Attrition reported (6/188); adherence NR	No	No, 182/186 analyzed; no mention cross-overs	No
Wahn 2003; Meltzer 2004 15 countries	Yes	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

Evidence Table 8. Quality assessment for seasonal allergic rhinitis trials in children

Author Year	Funding	Quality rating
Masi 1993	NR: third author affiliation is UCB Pharma Secotr R & D, B-1420 Braine-l'Alleud, Belgium	Fair
Pearlman 1997, Winder 1996 (safety) US	U.S. Pharmaceuticals Group, Pfizer, Inc.	Fair
Segal 2003	Pfizer Inc., New York, New York	Poor: post-randomization exclusions, exclusion of nasal congestions from TSS, baseline characteristics NR for entire group
Tinkelman 1996	U.S. Pharmaceuticals Group, Pfizer Inc,, New York, NY	Fair
Wahn 2003; Meltzer 2004 15 countries	Aventis Pharmaceuticals	Fair

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Study design Setting	Population Eligibility 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).
Active-control 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.
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

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Exclusion criteria	Allowed other medications/ interventions
Head-to-head trials		
Sienra-Monge 1999 Mexico Fair	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-control trials		
Cetirizine		
Hsieh J-C 2004 Taiwan Fair	A positive response to any other allergen; nasal abnormality, concurrent purulent nasal infection, any other significant medical condition.	Any current medication affecting any allergy symptom was discontinued as appropriate
Lai 2002 Taiwan Fair	Significant other medical condition which may have affected allergy symptoms	No

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Age Gender Ethnicity	Interventions	Method of outcome assessment and timing of assessment
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	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.
Active-control trials			
Cetirizine			
Hsieh J-C 2004 Taiwan Fair	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	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.
Lai 2002 Taiwan Fair	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	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

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Head-to-head trials			
Sienra-Monge 1999 Mexico Fair	NR/NR/80	NR/NR/78	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-control trials			
Cetirizine			
Hsieh J-C 2004 Taiwan Fair	NR/NR/65	4/1/60	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)
Lai 2002 Taiwan Fair	NR/ NR/ 80	11/ NR/ 69	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)

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Study design Setting	Population Eligibility criteria
Lee 2009 Taiwan	RCT, DB, placebo-controlled Single center - Chung Shan Medical University Hospital	PAR 6 to 12 yr; moderate to severe perennial allergic rhinitis for at least 1 yr. All were allergic to the house dust mite, which was confirmed by skin prick-test response and a positive reaction to mite specific IgE
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 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Exclusion criteria	Allowed other medications/ interventions
Lee 2009 Taiwan	Positive, response to other allergens or deformities of the ear, nose, or throat or infection during the 2 wk preceding the initial visit, or having taken medicine which may have affected any allergy symptoms such as antihistamine, decongestant or any form of steroid within seven days; had a respiratory tract infection or took the above medicine during the study period	Not allowed H1-antagonist, decongestant or any form of steroid
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.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Age Gender Ethnicity	Interventions	Method of outcome assessment and timing of assessment
Lee 2009 Taiwan	Mean age 8.4 yrs 58% male Ethnicity NR	Cetirizine vs. levocetirizine vs.placebo for 12 weeks	Daily diary of nasal symptom score (TSS), follow up at 4, 8 and 12 weeks also Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) at baseline and 12 weeks; Nasal peak expiratory flow rate (nPEFR) and laboratory examinations.
Placebo-controlled trials			
Cetirizine			
Baelde 1992 Belgium (Fair)	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	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.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Lee 2009 Taiwan	NR/NR/80	6/0/74	Cetirizine vs. levocetirizine vs.placebo Change at 12 weeks **TSS** -5.54(2.58)* ** vs. -3.30 (3.90) vs. -0.18 (1.77) Rhinorrhea -0.92 (0.54)* vs. -0.62 (0.95)* vs. -0.14 (0.28) Nasal decongestion -1.00 (0.39)* ** vs. -0.50 (0.65)* vs. -0.05 (0.32) Nasal itching -0.73 (0.81)* vs. -0.60 (0.95) vs. -0.11 (0.47) Sneezing -0.71 (0.53)* vs.-0.49 (0.74)* vs. -0.12 (0.28) Conjuctiva itching -1.06 (0.95)* vs. -0.82 (1.13)* vs. 0.01 (0.34) Tearing -0.22 (0.42)* **vs. -0.01 (0.33) vs. 0.00 (0.28) Conjunctiva hyperemia -0.79 (0.51)* ** vs. -0.42 (0.53)* vs. -0.02 (0.13) **PRQLQ -**19.73 (11.04)* vs. -24.09 (16.82)* vs. -1.63 (5.13) *Significant change compared with placebo (P < 0.05). **Cetirizine compared with levocetirizine (P < 0.05).
Placebo-controlled trials			
Cetirizine			
Baelde 1992 Belgium (Fair)	NR/NR/138	13/NR/125	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 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Study design Setting	Population Eligibility 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.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Exclusion criteria	Allowed other medications/ interventions
Ciprandi 2001 Italy (Fair)	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.	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.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Age Gender Ethnicity	Interventions	Method of outcome assessment and timing of assessment
Ciprandi 2001 Italy (Fair)	Mean age: 6.5y Range: 3-10y 75% male Ethnicity: NR	C: Cetirizine 5 mg qhs for 24w P: Placebo qhs for 24w	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.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Ciprandi 2001 Italy (Fair)	NR/NR/20	0/0/20	(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 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Study design Setting	Population Eligibility criteria
Placebo-controlled trials		
Cetirizine		
Chen 2006 Taiwan	DB RCT, single center	Documented clinical history of perennial allergic rhinitis (PAR) of at least half a year, a positive prick-test for house dust-mite and a positive mite-specific IgE, aged from 2 to 6 yr old
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.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Exclusion criteria	Allowed other medications/ interventions
Placebo-controlled trials		
Cetirizine		
Chen 2006 Taiwan	Corticosteroids or sodium cromoglycate within the past 4 wk, or H1-antagonist and/or decongestant within the past 7 days.	see exclusions
Jobst 1994 Germany, The Netherlands (Fair)	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.	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])

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Age Gender Ethnicity	Interventions	Method of outcome assessment and timing of assessment
Placebo-controlled trials			
Cetirizine			
Chen 2006 Taiwan	Mean age 4.5 yrs 53% male Ethnicity NR	Cetirizine vs. Montelukast vs. Placebo For 12 weeks	Patient diaries which included The Total Symptom Score (TSS) was the mean of eight symptoms, ranged from 0 to 3 on the scores for the previous 28 days at 4, 8, and 12 wk after treatment; the item of night sleep quality in the diary, in which symptoms were scored as follows: 0, slept well and did not wake up; 1, did not sleep too well or woke up once; 2, slept poorly or woke up two to three times; 3, slept very poorly or woke up more than three times and the PRQLQ
Jobst 1994 Germany, The Netherlands (Fair)	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	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.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Placebo-controlled trials			
Cetirizine			
Chen 2006 Taiwan	102/NR/60	0/0/60	Cetirizine vs. Montelukast vs. Placebo (SD) Change from baseline at week 12 **TSS** -0.60 (0.25)** vs -0.43 (0.23)** vs. -0.11 (0.12)- Nasal itching -1.07 (0.74)** vs. -0.48 (0.60) vs. -0.20 (0.17) Sneezing -0.72 (0.57)** vs. -0.56 (0.59)* vs. -0.08 (0.36) Rhinorrhea -0.56 (0.40)* vs. -0.49 (0.58)* vs. -0.10 (0.35) Nasal congestion -0.63 (0.40)** vs. -0.57 (0.43)* vs. -0.17 (0.24) Throat itching -0.26 (0.45) vs. -0.20 (0.47) vs. -0.05 (0.19) Conjuctiva itching -0.76 (0.49)** vs. -0.47 (0.57)* vs. -0.08 (0.29) Conjuctiva hyperemia -0.53 (0.41)* vs. -0.45 (0.54)* vs. -0.11 (0.26) Tearing -0.26 (0.28) vs. -0.22 (0.29) vs. -0.10 (0.14) **Night sleeping quality** -0.32 (0.15)** vs. -0.45 (0.17)** vs. -0.08 (0.0) **PRQL**Q -31.15 (23.36)** vs. -19.15 (20.71)* vs. -3.85 (5.56) Active vs. placebo *P ≤ 0.05, **P ≤ 0.001
Jobst 1994 Germany, The Netherlands (Fair)	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)	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

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Study design Setting	Population Eligibility criteria
Loratadine		
Potter 2005 South Africa	DB RCT, multicenter (24)	6 to 12 years who had PAR of at least 1 year's duration were included in the study, provided they were confirmed to be sensitive to house dust mite by a positive skin prick test result (wheal 3 mm larger than the diluent control for prick testing) or a positive Immunocap radioallergosorbent test result (class 3 or greater or 3.5 IU/mL) in the preceding 12 months.
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.
Azelastine		
Herman 1997 France	DB RCT, multicenter (18)	PAR 5 and 12 years and were skin prick positive to either house dust mites and/or cat or dog dander

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Exclusion criteria	Allowed other medications/ interventions
Loratadine		
Potter 2005 South Africa	Seasonal allergic rhinitis, with an ear, nose, or throat infection during the 2 weeks preceding the initial visit, or those with asthma that required corticosteroid treatment or a dermatologic condition that required antihistamine or topical corticosteroid treatment; vasomotor rhinitis, obstructive nasal polyposis, or obstructive deviation of the nasal septum and asthma that required corticosteroid treatment	No rescue meds allowed
Yang 2001 Taiwan (Fair)	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.	No
Azelastine		
Herman 1997 France	Severe total nasal blockage	Concomitant anti-allergic treatment was not permitted during the study; in addition, any concurrent medication which could interfere with the parameters evaluated in the study was not permitted.

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Age Gender Ethnicity	Interventions	Method of outcome assessment and timing of assessment
Loratadine			
Potter 2005 South Africa	Mean age 9.9 yrs 60.8% male Ethnicity NR	Placebo vs. Levocetirizine, 5 mg	The rhinitis symptoms were measured using a 4-grade scale, with scores ranging from 0 to 3 (0 indicates absent; and 3, severe) for each symptom. Symptoms were evaluated daily for each preceding 24 hours and recorded by the child or guardian on a daily record card. The mean T4SS was computed (sum of each individual symptoms score) for the initial 2 weeks of treatment and for the total treatment duration. PRQLQ at baseline and at each of the 3 subsequent clinic visits. Investigators also recorded their global evaluation of disease evolution for each patient at the end of the treatment period.
Yang 2001 Taiwan (Fair)	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	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.
Azelastine			
Herman 1997 France	Median age 8.71 yrs 60% male Ethnicity NR	Azelastine vs. placebo 6 weeks	Patient diaries assessed before and after a 2 week placebo washout phase and also following 2, 4 and 6 weeks of study medication. Symptoms evaluated were: Sneezing, nasal itch, rhinorrhea and nasal blockage

Evidence Table 9. Perennial allergic rhinitis trials in children

Author Year Country Quality score	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Loratadine			
Potter 2005 South Africa	371/NR/306	9/NR/306	Placebo vs. Levocetirizine Total 4 Symptoms Scores- mean (SD) baseline/2 weeks/4 weeks 7.51 (1.85)/6.75 (2.21)/6.19 (0.16) vs. 7.53 (1.85)/6.07 (0.15)/5.59 (0.16) Difference (95% CI) vs placebo at 2 weeks 0.69 (0.27–1.12) P= 0.001 and 4 weeks 0.61 (0.16–1.06) P = 0.008 50% Response Rates- mean (SD) 2 weeks/4 weeks 3.9% /11.2% vs. 12.3% / 17.5% OR (95% CI) Two weeks 3.42 (1.33–8.83) P = 0.01, Four weeks 1.69 (0.88–3.24) P = 0.12 Investigator rated markedly or moderately improved 44.7% vs. 57.1% P = NS
Yang 2001 Taiwan (Fair)		NR/NR/46	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
Azelastine			
Herman 1997 France	NR/NR/125	8/NR/125	Results shown in graphs - Compared to the baseline, for each of the six study weeks, the reduction in the VAS scores for all four symptoms (sneezing, nasal blockage, nasal itch and rhinorrhea) was statistically greater (P = 0.0001) for the azelastine group compared to the placebo group

Evidence Table 10. Quality assessment of 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?**
Baelde et al, 1992 Belgium	Yes	Method not reported	Yes	Yes	Yes; described as 'double blind' but unclear who	Yes
Chen et al, 2006 Taiwan	Method not reported	Method not reported	Yes	Yes	Described as "double blind"	Described as "double blind"
Ciprandi et al, 2001 Italy	Method NR	Method not reported	Yes (no statistics)	Yes	Yes; described as 'double blind' but unclear who	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
Herman, 1997	Method not reported	Method not reported	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"
Hseih 2004 Taiwan	Yes	Method NR	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"
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
Lee et al, 2009 Taiwan	Method not reported	Method not reported	Yes	Yes	Described as "double blind"	Described as "double blind"
Lai 2002 Taiwan	Yes	Method not reported	Yes	Yes	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

Evidence Table 10. Quality assessment of perennial allergic rhinitis trials 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
Baelde et al, 1992 Belgium	Yes	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
Chen et al, 2006 Taiwan	Described as "double blind"	Attrition was reported, the rest was not reported	No; all completed study	All completed study	No
Ciprandi et al, 2001 Italy	Yes	Attrition and adherence yes, contamination no.	Attrition 0	Yes	No
Ciprandi et al, 2004 Italy	Study described as 'double blind' but unclear who was blinded	None reported	NR	Unclear; insufficient information	NR
Herman, 1997	Yes	Number completed reported 117/125 = 94% No report of crossover, adherence, contamination	No	No Lost data was not included in ITT	NR
Hseih 2004 Taiwan	Yes	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
Jobst et al, 1994 Germany, The Netherlands	Study described as 'double blind' but unclear who was blinded	Attrition and compliance yes, contamination no	No	No (328/330 analyzed)	One patient withdrawn for protocol violation
Lee et al, 2009 Taiwan	Described as "double blind"	Attrition was reported, the rest was not reported	6/80 (7.5%) dropped	NR	Yes, exclusions based on not having TSS recordings
Lai 2002 Taiwan	NR; study reported as 'double blind"	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
Pearlman et al, 1997, Winder et al, 1996 (safety) US	Yes	Yes.	No.	No (205/209 analyzed)	No.

Evidence Table 10. Quality assessment of perennial allergic rhinitis trials in children

Author Year Country	Funding	Quality rating
Baelde et al, 1992 Belgium	NR, affiliation of authors is UCB Pharma Sector (Research and development), Braine-l'Alleud, Belgium	Fair
Chen et al, 2006 Taiwan	None	Fair
Ciprandi et al, 2001 Italy	NR	Fair
Ciprandi et al, 2004 Italy	NR	Poor: no information on attrition or baseline comparability
Herman, 1997	Asta Medica AG, Frankfurt, Germany	Fair
Hseih 2004 Taiwan	NR	Fair
Jobst et al, 1994 Germany, The Netherlands	NR; senior author (H van deVenne) affiliated with UCB, Pharma Sector, research and Development, Belgium	Fair
Lee et al, 2009 Taiwan	NR	Fair
Lai 2002 Taiwan	Research grant of Chung Shan Medical University	Fair
Pearlman et al, 1997, Winder et al, 1996 (safety) US		Fair

Evidence Table 10. Quality assessment of 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?**
Potter 2005 South Africa	No	No	Yes	Yes	NR; study reported as 'double blind"	NR; study reported as 'double blind"
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"
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"
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

Evidence Table 10. Quality assessment of perennial allergic rhinitis trials 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
Potter 2005 South Africa	Yes	Dropout rate and compliance rate reported	NR	NR ITT no clearly defined; "ITT population" referred to, implying perhaps not all randomized	NR
Sienra-Monge 1999 Mexico	Yes	Attrition (2/80, both in group A)	No (2.5%)	No, 2 cetirizine patients withdrew due to AEs, not analyzed	No
Sienra-Monge et al, 1999 Mexico	Unclear; reported as "double blind"	Attrition yes, others no	No	No (2/80 not analyzed). Did not analyze patients who experienced adverse effects (considered treatment failures)	No
Yang et al, 2001 Taiwan	Study described as 'double blind' but unclear who was blinded	Attrition and adherence yes, contamination no	High (23%) withdrew, but NSD between groups	No (46/60 analyzed)	No

Evidence Table 10. Quality assessment of perennial allergic rhinitis trials in children

Author Year Country	Funding	Quality rating
Potter 2005 South Africa	UCB Farchim Chemin de Croix blanche, Bulle, Switzerland	Poor
Sienra-Monge 1999 Mexico	Glaxo/Welcome Mexico	Fair
Sienra-Monge et al, 1999 Mexico	Glaxo/Welcome Mexico SA de CV, Col San Lorenzo Huipulco, Mexico	Fair
Yang et al, 2001 Taiwan	Schering-Plough	Fair

Evidence Table 11. Urticaria trials in children

Author Year Country (Quality rating)	Study design Setting	Population Eligibility criteria	Exclusion criteria	Age Gender Race/ethnicity
Active-control 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 11. Urticaria trials in children

Author Year Country (Quality rating)	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Active-control trials			
La Rosa 2001 Italy Fair	C: Cetirizine: 5 mg qd (n=31) O: Oxatomide: 25 mg qd (n=31)	No	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
Placebo-controlled trials			
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	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

Evidence Table 11. Urticaria trials in children

Author Year Country (Quality rating)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Results
Active-control trials			
La Rosa 2001 Italy Fair	NR/ NR/ 62	5/ NR/ 57	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 trials			
Simons 2001, Simons 1999 Europe and Canada ETAC study Fair	NR/NR/817	26/73/797 at 18m, 694 at 24m	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 12. 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?**
La Rosa 2001 Italy	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
Simons 2001, Simons 1999 Europe and Canada ETAC study	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

Evidence Table 12. Quality assessment of urticaria trials 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
La Rosa 2001 Italy	Yes	Attrition reported (5/62)	No	No, 57/62 analyzed; no mention cross-overs	No
Simons 2001, Simons 1999 Europe and Canada ETAC study	Yes	Attrition reported, others not	No; 12% over 18 months, no differential	No; attrition 99/817	NR

Evidence Table 12. Quality assessment of urticaria trials in children

			External validity				
Author Year Country	**Funding**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Relevance**
La Rosa 2001 Italy	UCB Laboratories, Pianezza, Torino, Italy	Fair	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 Europe and Canada ETAC study	UCB, SA (Belgium)	Fair	NR/NR/817	None; None	NR	NR	Young children (12-24 months)

Evidence Table 13. Adverse events in observational studies

Author Year	Study outcomes Characteristics	Results
Augustin 2009	Safety and efficacy in chronic idopathic Urticaria (CIU) N=9246, 62.5% female, mean age 43.2 , mean duration of CIU 24.9 months % of patients with previous treatment with antihistamine: ceterizine 32.7%, loratadine 28.0%, fexofenadine 15.8%, "another" antihistamine 30.7% Mean duration of treatment: 40.4 yrs Intervention: Desloratadine Post marketing surveillance study	Change in Itching/pruritus at follow-up: p<0.0005 (% of patients) decreased severity of itching from baseline: 83.4% no change in itching from baseline: 15.3% worsening of itching at follow up: 1.3% Change in general state of urticaria at follow-up : p<0.0001 (% of patients) severe: 2.3%, moderate: 11.3%, mild: 43.2%. no: 43.2% % patients with no sleep disturbance due to CIU: (p<0.0001) No sleep disturbance: 70.3%, mild : 20.5%, moderate: 6.8%, severe: 1.9% Impairment of daily activtities due to CIU, change from baseline (p<0.0001) No impairment: 67.2%, mild 24.6%, moderate: 6.8%, severe: 1.5% Response to therapy-complete response: 42.7%, 5.6% had significant relief, moderate response: 11.7% AE: headache 0.13%, fatigue: 0.11%, dry mouth: 0.06%. therapy was stopped 0.2%
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 13. Adverse events in observational studies

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).
Gastpar 1993	Long term efficacy and tolerability of patients with PAR, open uncontrolled design Initial 6 months: Azelastine nasal spray 0.56 mg/d N: 185, % male: 54.1%, age: 37.2 (13.0) Long term treatment for 30-60 weeks: Dose 0.56mg/day N: 35, male:48.6%, 34.0 (11.5) Mean TSC score at baseline: 11.56	Initial 6 months total withdrawals N(%)/Withdrawals due to AE,N (%): 24 (13%)/5 (2.7%) Improvement in total rhinitis symptom score, p< 0.001 highest rate of improvement in 1st month-data in graph Global assessment of efficacy : 84.1% recorded "very good" or "good" Global assessment of tolerability:95.6% "very good" or "good" At wk 6, reduction from baseline in symptoms of: Stuffy nose 72.8, Itchy nose 69.4, Rhinorrhoea 64.6, Sneezing 57.3. Others reported in Table. Follow:up 30-60 wks Incidence of Hyperplasia N(%): 2/21 (9.5%) mean TSC score at month 21: 7 Global assessment of efficacy : 33 (94.3%) recorded "very good" or "Good" Global assessment of tolerability: 35 (100%) recorded "very good" or "good"

Evidence Table 13. Adverse events in observational studies

Author Year	Study outcomes Characteristics	Results
Layton 2006	levoceterizine vs desloratadine N: 12367 vs 11828 Median age[interquartile range]: 37[22-55], 37[22-54] % female: 58.2 vs 59.9 allergic rhinitis with asthma and wheezing (%): 12.9 vs 15.3% (p<0.0001) allergic rhinitis without asthma and wheezing (%): 54.1 vs 52.3 other (%): 28.7 vs 28.0, not known (%): 4.3 vs 4.4 Use of antihistamine in previous 12 months: 31.9 vs 29.3 use of antihistamine in previous 12 months not known: 17.5 vs 18.6	Levoceterizine vs desloratadine incidence of first ocurance of drowsiness/sedation: 0.37 vs 0.08, p<0.0001 Sex-adjusted OR for drowsiness sedation for patients with allergic rhinitis without asthma/wheezing: OR 6.75; 95% CI 2.37, 19.22 , n=12,627, estimate-statistically significant Sex-adjusted Or for allergic rhinitis with asthma/wheezing: OR 3.51 ;95% CI 0.71, 17.43, n=3347; estimate: NS Sex-adjusted OR for "other" indication: OR 3.11; 95% CI 0.86, 11.31, n=6725, estimate: NS
Layton 2009	N=11828, median age 37 yrs, 59.9% female allergis rhinitis: 52.3%, allergic rhinitis with asthma/wheezing : 15.3%, urticaria: 17%, other conditions (e.g. allergy): 11% Desloratadine treatment 97% initially prescribed 5mg/day, 3% prescribed 10mg/day, <1% prescribed ≥ 15mg/day and 2.5mg /day	Most frequently reported events in first 2 months Drowsiness: 0.07%, headache 0.21%, Migraine 0.04%, Sedation 0.03%, Synocope (0.02%)

Evidence Table 13. Adverse events in observational studies

Author Year	Study outcomes Characteristics	Results
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.
Pedersen 2006	Risk of hypospadias after exposure to loratadine and other antihistamines Nested case-control design based on women enrolled in the Danish National Birth Cohort from 1998-2002 (n≈ 95,000 pregnant women) Data on maternal use of medicine in pregnancy were retrieved from questionnaires and telephone interviews, and outcome data were obtained from the National Hospital Discharge Registry A total of 203 cases of hypospadias, recorded within the first year post-partum, were identified. Ten male controls were randomly selected per case and matched by DOB (n=2030 controls)	Cases # (%)/Controls # (%) Exposure to loratadine*: 1 (0.5)/25 (1.2) 30 days before conception and 1st trimester: 1 (0.5)/12 (0.6) Second trimester: 0 (0)/8 (0.4) Third trimester: 0 (0)/13 (0.6) Exposure to other antihistamines*: 30 days before conception and 1st trimester: 4 (2.0)/48 (2.4) Second trimester: 2 (1.0)/37 (1.8) Third trimester: 2 (1.0)/11 (0.5) *Reported exposure during pregnancy or up to 30 days before conception In total, 146 of 203 cases were diagnosed with hypospadias within 6 months postpartum, and none had reported exposure to loratadine during the entire pregnancy or up to 30 days before conception The association between hypospadias recorded anytime postpartum and maternal use of antihistamines (adjusted OR* (95% CI): Exposure within the first trimester or up to 30 days before conception: Loratadine: 0.9 (0.1-6.4) Other antihistamines was 0.5 (0.1-1.9) Exposure within the entire pregnancy or up to 30 days before conception: Loratadine: 0.4 (0.1-2.8) Other antihistamines: 0.7 (0.3-2.1) *Adjusted for maternal age, maternal smoking, birth order, gestational age, preeclampsia, and use of ovulation-inducing drugs, anti-epileptics, or antibodies

Evidence Table 13. Adverse events in observational studies

Author Year	Study outcomes Characteristics	Results
Weber-Schoendorfer 2008	Safety of cetirizine during 1st trimeser of pregnancy Inclusion: women whose physician contacted teratology information service (TIS) reporting 1st trimester exposure to cetirizine between 1992-1996 Data was collected via questionnaires administered during early pregnancy and 8 weeks after expected delivery date, and a pediatric exam was conducted at 6 weeks n=196 pregnant women with first trimester exposure to cetirizine n=1686 controls cetirizine/controls median age (y): 31/31	Major birth defects were not more common in the cetirizine group than in the control group (OR 1.07, C 0.21-3.59). The study also compared the crude rate of spontaneous abortions (OR 0.97, CI 0.54-1.65), of preterm deliveries (OR 1.07, CI 0.35-1.5), and the birth weight of term newborns (p=0.13) Pregnancy Outcomes: cetirizine (%)/controls(%)/exposed vs controls OR (CI)/exposed vs controls p-value Exposed pregnancies: 196/1686/-/- Spontaneous abortion-crude rates: 8.9/9.1/0.97 (0.54-1.65)/1.00 Preterm births: 5.6/7.3/0.76 (0.35-1.5)/0.54 All birth defects: 7.7/5.7/1.36 (0.7-2.45)/0.32 Major birth defects: 1.7/1.6/1.07 (0.21-3.59)/0.76 Mean gestational age at delivery (weeks), term births: 39.82/39.81/-/0.89 Mean birth weight (grams), term births: 3413/3473/-/0.13

Evidence Table 13. Adverse events in observational studies

Author Year	Study outcomes Characteristics	Results
Wober 1997 Arzneim-Forsch/Drug Res.	Efficacy and safety of a nasal spray containing azelastine Post-marketing drug surveillance program n=211 children under 13 years of age Median age: 11 years (range 3-12) Gender (% male): 59	<u>All-symptom-sum-score subgroups:</u> Mean score/Score in the lowest subgroup (%) Baseline visit: 11.03/4 Control visit: 3.21/84 A decrease of the all-symptom score was seen in 98.2% of patients and an increase was seen in 1.8% of cases. <u>Nose-symptom-sum-score subgroups:</u> Mean total score/Score in the lowest subgroup (%) Baseline visit: 7.64/13 Control visit: 2.31/91 A decrease of the total nasal score was seen in 98% of patients and an increase was seen in 2% of cases. <u>Eye-symptom-sum-score subgroups:</u> Mean total score/Patients with no ocular symptoms (%) Baseline visit: 2.25/34 Control visit: 0.48/79 A decrease of the total ocular score was seen in 62% of patients and an increase was seen in 1 patient There were no signicifant differences in the changes of either the total symptom scores, total nasal scores, or total occular scores, when stratified by age, sex, pretreatment, and concomitant medication <u>Frequency of adverse events:</u> n (%)/n azelastine discontinued Pruritis: 5 (2.4)/1 Headache: 2 (1)/1 Parasthesia:2 (1)/0 Dry mouth: 1 (0.5)/0 Earache: 1 (0.5)/0 Taste perversion: 6 (2.8)/1 Rhinitis: 5 (2.4)/1 Not specific: 2 (1)/1 Total: 24 (11.4)/6

Evidence Table 13. Adverse events in observational studies

Author Year	Study outcomes Characteristics	Results
Wober 1997 Curr. Med. Res. Opin	Efficacy and tolerability of azelastine nasal spray Post-marketing surveys to rate symptoms and answer treatment questions were administered at 14 days (study 1) and 31 days (study 2) <u>Study 1</u> n=3680 Recruitment: January-July 1993 Median age: 31 years (range 7-90) Gender (% male): 48.8 <u>Study 2</u> n=4002 Recruitment: October 1993-January 1994 Median age; 31 years (range 3-85) Gender (% male): 50.9	**Efficacy** Sum score means (±SD) for symptoms before and after treatment: <u>Study 1</u> Before/After/X^2 Total symptoms: 13.3 (±5.3)/2.9 (±3.4)/2073.1 Nose symptoms: 8.5 (±2.8)/2.0 (±2.2)/1984.3 Eye symptoms: 3.1 (±2.41)/0.6 (±1.17)/871.7 <u>Study 2</u> Before/After/X^2 Total symptoms: 11.0 (±4.9)/3.0 (±3.4)/2008.5 Nose symptoms: 7.9 (±2.8)/2.3 (±2.3)/1929.2 Eye symptoms: 2.0 (±2.2)/0.4 (±1.1)/492.1 **Tolerability** Incidence of all adverse reactions reported during treatment: Study 1/Study 2 Number (%) Total:260 (7.1)/350 (8.7) Taste disturbance:88 (2.4)/97 (2.4) Rhinitis: 77 (2.1)/159 (4.0) Application site reaction: 52 (1.4)/47 (1.2) Somnolence: 17 (0.5)/12 (0.3) Headache: 13 (0.4)/6 (0.1) Epistaxis: 8 (0.2)/13 (0.3) Dry mouth: 6 (0.2)/13 (0.3)

Evidence Table 14. Quality assessment of observational studies

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?	Overall quality
Craig-McFeely 2001	N/A	8.7% non-evaluable forms	Yes	Yes	Yes	Yes	Yes	Fair
Augustin 2008	Method of pt recruitment was not reported. This was a post-marketing surveillance study	N/A	Unclear	Spontaneous reporting of harms	Spontaneous reporting of harms	No	range 1-238 days	Fair-Poor
de Abajo 1999	Yes	Yes low loss to f/u 5% missing	Yes	Yes	Yes	Yes	Yes f/u 5 years	Fair
Finkle 2002	N/A	N/A	Yes	Yes	Yes	NR	Yes	Fair
Gastpar 1993	NR, unknown how pts were recruited	Low for 1st 6 mo, but high for study extension period (21.7% of pts continued with extension)	No. Possibly by spontaneous reporting.	Yes, specifically stated by spontaneous reporting	Unknown. In addition to spontaneous reports, lab f/u, and assessment of vitals, global assessment by investigators was performed.	No	Initial= 6 mos, then addnal 30-60 weeks	Fair

Evidence Table 14. Quality assessment of observational studies

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?	Overall quality
Layton 2006	Used prescription event monitoring method. Pts were identified from NHS which was supplied by PPA in England	N/A	NR but events were categorized using DSRU terms	Questionnaires	Possibly if questionnaires were only used	Yes	at least 6 mos	Fair
Layton 2009 (Examining…)	Used National Prescription Processing Centre in England for scripts issued by GPs between March 2001-May 2001.	N/A	Unclear	Yes	Possibly (GPs were to report events and then f/u was done as needed)	Yes	No, most were >15 days and data reported for 1st 2 mos	Fair
Mann 2000	N/A	NR	Yes	Yes	Yes	Yes	Yes	Fair
Pederson 2006	From National Hosp Discharge Registry & Danish National Birth Cohort via unique registry number and also used ICD-10 codes	N/A	Yes	Questionnaires and telephone interviews	Possibly depending on if a script was used for phone interviews but method was not described	Yes	Interviews 3 and 4 were done when child was 6 and 18 months of age	Fair
Weber-Schoendorfer 2008	Potential for bias. Enrolled women who/whose MD contacted teratology info service	NR	Yes	Unclear. Questionnaires used but other methods were used to obtain info about pregnancy complications, etc	Unclear	No	50% >7 weeks, 25% >9 weeks; 83% took only during 1st trimester	Fair-Poor

Evidence Table 14. Quality assessment of observational studies

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?	Overall quality
Wober 1997 (Children)	Unclear. Suspect there was potential for bias as data appears to be from another trial by Wober in 1997	NR	No. Possibly by spontaneous reporting. Later events were categorized by systems	NR for harms (possibly spontaneous reporting)	NR	No	No, 2-4 weeks	Fair-Poor
Wober 1997 (Composite)	Potential for bias. Community physicians recruited pts for post-marketing survey but method of recruitment were not described	NR	No. Possibly by spontaneous reporting. Later events were categorized by systems	NR for harms (possibly spontaneous reporting)	NR	No	No, 2-4 weeks	Fair-Poor

Evidence Table 15. 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 15. Adverse events from efficacy trials in adults

		Internal validity				
Author Year Country	**Total withdrawals; withdrawals due to adverse events**	**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?**
Seasonal allergic rhinitis						
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
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
Ciprandi 1997 Italy	0 / 0	Yes	Yes	Yes	Yes, diary	Yes
Corren 2005 USA	8; 6 (2 in cetirizine, 4 in azelastine)	Unclear, methods NR	Yes	No	Yes	Unclear

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Seasonal allergic rhinitis		
Berger 2003	No	Yes
Bernstein 2004 USA	NR	Yes (4 weeks)
Ciprandi 1997 Italy	NR	Yes, all patients completed
Corren 2005 USA	NR	Yes (2 weeks)

Evidence Table 15. 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 15. Adverse events from efficacy trials in adults

		Internal validity				
Author Year Country	**Total withdrawals; withdrawals due to adverse events**	**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?**
Dockhorn 1987	NR; NR	Yes	Yes	No	Yes	Yes
Hampel 2003 USA	total withdrawals=16; 6/16 for AEs	Yes	Yes	Yes	Yes, diary	Yes

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Dockhorn 1987	No	Yes
Hampel 2003 USA	NR	Yes

Evidence Table 15. 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 15. Adverse events from efficacy trials in adults

		Internal validity				
Author Year Country	**Total withdrawals; withdrawals due to adverse events**	**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?**
Hampel 2004 USA	100 pts ; 20 pts (2.7%)	Unclear, methods NR	13%	No	No	Unclear
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
Martinez-Cocera 2005 Spain	37/12	Unclear, methods NR	No (15%)	No	No	Unclear

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Hampel 2004 USA	Baseline variables used as covariates in analyses	Yes (4 weeks)
Howarth 1999 UK, US, France	No	NR
Martinez-Cocera 2005 Spain	Yes	Yes (2 weeks)

Evidence Table 15. 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 15. Adverse events from efficacy trials in adults

		Internal validity				
Author Year Country	**Total withdrawals; withdrawals due to adverse events**	**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?**
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
Prenner 2000 USA	NR; NR	Yes	Yes	No	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

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Okubo 2004, 2005 Japan	Yes	Yes (2 weeks)
Prenner 2000 USA	No	Yes
Ratner 2004 USA	Yes, baseline groups differed on duration of allergy symptoms; baseline factors used as covariates	Yes (4 weeks)

Evidence Table 15. 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 15. Adverse events from efficacy trials in adults

		Internal validity				
Author Year Country	**Total withdrawals; withdrawals due to adverse events**	**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?**
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
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
van Cauwenberge 2000 Europe and South Africa	71; 15	Yes	Yes	No	Yes	No

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Saint-Martin 2004 France	Yes, center and basal SS used as covariates	Yes (2 weeks)
van Adelsberg 2003 USA	No	Yes (4 weeks)
van Cauwenberge 2000 Europe and South Africa	No	Yes

Evidence Table 15. 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.
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 15. Adverse events from efficacy trials in adults

		Internal validity				
Author Year Country	**Total withdrawals; withdrawals due to adverse events**	**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?**
Urticaria						
Breneman 1996	43; 3	Yes	Yes	Yes	Yes, diary	Yes
Guerra 1994 Italy	NR ; 1 pt withdrew due to AEs	Yes	No	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
Kaplan, 2005 USA	25; NR	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

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Urticaria		
Breneman 1996	NR	Yes
Guerra 1994 Italy	NR	Yes
Handa 2004 India	NR	Yes (2 weeks)
Kaplan, 2005 USA	See QA table	See QA table
Monroe, 2003 International	Yes (RCT)	Yes (6 weeks)

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Method and timing of assessing adverse events	Adverse events
Perennial allergic rhinitis		
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 15. Adverse events from efficacy trials in adults

		Internal validity				
Author Year Country	**Total withdrawals; withdrawals due to adverse events**	**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?**
Perennial allergic rhinitis						
Frolund 1990	25 pts; 1 pt	Yes	Yes	Yes	Yes, diary	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

Evidence Table 15. Adverse events from efficacy trials in adults

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Perennial allergic rhinitis		
Frolund 1990	NR	Yes
Simons 2003 US and Canada	Yes (RCT)	Yes (4 weeks)

Evidence Table 16. 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
Kulthanan 2001	Time series, open-label, uncontrolled. 5 medical school hospitals in Thailand.	At least 12 years old with symptoms of urticaria at least 3 times per week for not less than 6 consecutive weeks without apparent causes.	Women who were not using adequate contraceptive measures or breast feeding or with pregnancy, patients with cardiac, renal, hepatic, or rapidly progressing fatal diseases, history of alcohol consumption, drug abuse, or hypersensitivity to fexofenadine or terfenadine, mental conditions rendering them incapable fo understanding the nature, scope, and possible consequences of the study and/or evidence of an uncooperative attitude.

Evidence Table 16. 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)
Kulthanan 2001	Of patients who completed (98/108): mean age 35.7 (SEM 1.3, range 14-87) 22.4% male	Fexofenadine 120 mg (60 mg twice daily) for 6 weeks	NR	At each of three visits (end of week 1, 3, and 6) all patients or observed AEs were recorded.	AEs occurred in 20 patients (18.5% of 108 cases), or 23 events. One patient withdrew due to headache. Most common AEs were headache and drowsiness (8 events each; 7.4%); others were dizziness (3 events), increased appetite (2 events), increased weight, and cough (1 event each). Degree of treatment-related AEs was mainly graded as mild. Drowsy visual analogue scale analysis showed a slight increase in the first few weeks of treatment (data presented graphically only).

Evidence Table 17. Quality assessment of adverse events in observational studies in adults

Author Year	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, no for others	Yes	No (not blinded)	No	Yes (6 weeks)	Fair	Aventis Pharma Ltd.

Evidence Table 18. Adverse events in adult allergic rhinitis trials with follow-up of less than 14 days

Author Year Country	Method of assessing adverse events	Total withdrawals/ Withdrawals due to adverse events	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
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	Yes	Unclear, reported as double blind
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	Yes	Unclear, reported as double blind
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	Yes	Unclear, reported as double blind
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	Not clear	Unclear, reported as double blind
Hyo et al. 2005	Not reported	Not reported	No	No	Unclear, reported as double blind
Lee et al. 2004	Not reported	Not reported	No	No	Not reported

Evidence Table 18. Adverse events in adult allergic rhinitis trials with follow-up of less than 14 days

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Funding
Day et al. 1997	Yes (RCT, similar groups at baseline)	No for most AEs (single dose)	Nordic Merrell Dow, Quebec
Day et al. 1998	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 (RCT, similar groups at baseline)	No for most AEs (2 days)	Pfizer
Horak et al. 2005	No	No for most AEs (single dose)	UCB Farchim, Bulle, Switzerland
Hyo et al. 2005	Yes (RCT, similar groups at baseline)	No for most AEs (2 days)	NR
Lee et al. 2004	No	Unclear (1 week)	University of Dundee departmental grant, no funding from pharmaceutical industry.

Evidence Table 18. Adverse events in adult allergic rhinitis trials with follow-up of less than 14 days

Author Year Country	Method of assessing adverse events	Total withdrawals/ Withdrawals due to adverse events	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
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	Yes	
Passalacqua et al. 2004	Not reported	None	No	No	Not reported
Satish et al. 2004	Not reported	Total: 4/48 (8.3%) AEs: Not reported	No	No	Not reported
Simons et al. 2000	Patients asked about sleepiness, dry mouth, and other possible adverse events of the medication.	No withdrawals	Yes	Yes	Unclear, reported as double blind
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	No	Not reported

Evidence Table 18. Adverse events in adult allergic rhinitis trials with follow-up of less than 14 days

Author Year Country	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Funding
Meltzer et al. 1996	Yes (RCT, similar groups at baseline)	No for most AEs (2 days)	Pfizer
Passalacqua et al. 2004	No	No for most AEs (single dose)	Associazione Ricerca Malattie Immunologiche e Allergiche.
Satish et al. 2004	No	No for most AEs (3 doses)	Research support from Integrated Therapeutics Group, Inc.
Simons et al. 2000	No	No for most AEs (single dose)	NR
Weiler et al. 2000	No	No for most AEs (single dose)	Grant from Hoescht Marion Roussel and from NIH.

Evidence Table 19. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse events	Total withdrawals; withdrawals due to 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	2 pts; 2 pts (2 pts in cetirizine group,1 with mild irritability and 1 with generalized rash)
Active-control 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	4; 0
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.	5;0
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	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)

Evidence Table 19. Adverse events in efficacy trials in children

Author Year Country	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	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-control trials							
Boner 1989	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	Unclear; no information on patient selection	Yes	No	Yes	Unclear	No	Yes (3 months)
Jordana 1996	Unclear; no data on selection of patients	Yes, for ITT analysis	No	No	Unclear; blinding of assessor NR	No	Yes (4 weeks)

Evidence Table 19. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse events	Total withdrawals; withdrawals due to AEs
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)	0; 1
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%	4; reasons for withdrawals NR
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%	6, including 2 for an upper respiratory tract infection, 1 for personal reason, 1 for unknown reason

Evidence Table 19. Adverse events in efficacy trials in children

Author Year Country	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?
La Rosa 2001	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	Unclear; no data on selection of patients	29526	No	No	Unclear; blinding NR	NR, but baseline groups comparable for known confounders	Yes (12 weeks)
Tinkelman 1996	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 19. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse events	Total withdrawals; withdrawals due to 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%	3 pts (1 on cetirizine, 2 on 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	4; 0
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	None
Ciprandi et al, 2001 Italy	NA (AE NR)	None	0
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	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)

Evidence Table 19. Adverse events in efficacy trials in children

Author Year Country	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 trials							
Allegra 1993	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	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	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							
Jobst et al 1994	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 19. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse events	Total withdrawals; withdrawals due to 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%	10; 3 3 AE withdrawals: 2 on cetirizine (from headache, vertigo, and autonomic symptoms); 1 on placebo for lipothymia
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	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)

Evidence Table 19. Adverse events in efficacy trials in children

Author Year Country	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	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	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 19. Adverse events in efficacy trials in children

Author Year Country	Method of assessing adverse events	Adverse events	Total withdrawals; withdrawals due to 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	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
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	3 children in fexofenadine-treated group withdrew from study, but not considered to be related to treatment (asthma, upper respiratory infection, vomiting); one fexofenadine-treated group developed neutropenia felt to be related to treatment, child recovered completely
Yang et al 2001	NR	No adverse event was recorded	None

Evidence Table 19. Adverse events in efficacy trials in children

Author Year Country	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	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	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	Unclear; no data on selection of patients	14/60	No	No	Unclear; investigator recorded AE from patient at each visit	NR	Yes (3 weeks)

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility 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.

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Exclusion criteria	Age Gender Race/ethnicity
Placebo-controlled trials		
Cetirizine		
Simons 2003 US and Canada (Fair)	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.	Mean age 8 months (range 6 to 11 months) 48% male Ethnicity NR

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Interventions	Allowed other medications/ interventions
Placebo-controlled trials		
Cetirizine		
Simons 2003 US and Canada (Fair)	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 20. 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 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Adverse events	Total withdrawals; withdrawals due to 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).	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 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility 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.
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.

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Exclusion criteria	Age Gender Race/ethnicity
Winder 1996 (Fair)	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.	Mean age: 8.85y Range: 6-11 y 66.7% male 88.4% white 10.6% other
Placebo-controlled trials		
Desloratadine		
Bloom 2004 USA 2-5y arm (Fair)	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.	Mean: 3.45y 55.8% male White: 23.4% African American: 75.7% Other: 1.0%

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Interventions	Allowed other medications/ interventions
Winder 1996 (Fair)	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)	15-day treatment 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 20. 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 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Adverse events	Total withdrawals; withdrawals due to 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	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)	*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	NR; NR

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility 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.
Prenner 2006 United States, Latin America, and South Africa	Randomized, double-blind, parallel group, Multicenter (29)	Girls and boys 6 months of age to less than 2 years of age, candidates for antihistamine therapy or who had a history of antihistamine therapy, experienced at least one of the following signs or symptoms in the absence of a known, infectious, treatable condition (such as scabies or other infection that would require specific nonantihistaminic treatment): itchy nose, sneezing, rhinorrhea, tearing or redness of the eyes, or itchy skin and in general good health

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Exclusion criteria	Age Gender Race/ethnicity
Bloom 2004 USA 6-11y arm	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.	Mean: 8.2y 43.3% male White: 41.7% African American: 56.7% Other: 1.7%
Prenner 2006 United States, Latin America, and South Africa	Allergic to or could not tolerate antihistamines or if they had a history of hypersensitivity to the study medication or any of its excipients, any patient with a recent history of upper respiratory tract or sinus infection that necessitated antibiotic therapy (within the 14 days) or viral upper respiratory infection (within 7 days), received any investigational drug within the 30 days or who had previously been randomly assigned into the study, as was any child related to investigational staff directly involved with the study at the investigational study site; evidence of clinically significant hematopoietic, cardiovascular, hepatic, renal, neurologic, psychiatric, autoimmune, or other disease.	Mean age 13 months 51% male 23% White 7% Black 66% Hispanic 2% Asian 2% Other

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Interventions	Allowed other medications/ interventions
Bloom 2004 USA 6-11y arm	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
Prenner 2006 United States, Latin America, and South Africa	Desloratadine syrup (0.5 mg/mL; 1.0 or 1.25 mg orally once daily, depending on age) or placebo for 15 days	Corticosteroids, and nasal or inhaled cromolyn sodium or nedocromil, high-potency topical corticosteroids, and systemic antibiotics, for prophylactic therapy at stable doses or for treatment of nonrespiratory infection

Evidence Table 20. 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
Prenner 2006 United States, Latin America, and South Africa	Diary cards that were completed by the parent/guardian and were reviewed by the investigator at each visit; Baseline, pretreatment 12-lead ECG, recording ventricular rate (VR) and PR, QRS, QT, and QTc intervals, were completed at the screening visit and days 8 and 15 and physical examination was performed at the screening visit and again on days 8 and 15.	NR/NR/255 randomized	9/0/253

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Adverse events	Total withdrawals; withdrawals due to 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	NR; NR
Prenner 2006 United States, Latin America, and South Africa	Desloratadine vs. Placebo Any adverse effect 34 (26.0) vs. 27 (21.8) Anorexia 4 (3.1) vs. 2 (1.6) Increased appetite 3 (2.3) vs. 3 (2.4) Fever 4 (3.1) vs. 1 (0.8) Somnolence 7 (5.3) vs. 9 (7.3) Diarrhea 8 (6.1) vs. 3 (2.4) Insomnia 3 (2.3) vs. 0 Irritability 9 (6.9) vs. 7 (5.6) Respiratory system disorders Bronchitis 1 (0.8) vs. 0 Coughing 2 (1.5) vs. 2 (1.6) Epistaxis 1 (0.8) vs. 0	9 withdrawals, 2 placebo and 7 desloratadine 3 due to Aes, 2 placebo, 1 desloratadine

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility criteria
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.

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Exclusion criteria	Age Gender Race/ethnicity
Placebo-controlled trials		
Loratadine		
Grimfeld et al 2004 International (51 centers) Preventia I Study (Fair)	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).	Mean age: 23.95 months Range: 60.7% male White: 73.2% Black: 0.7% Hispanic: 18.2% Asian: 6.6% Other: 0.5%

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Interventions	Allowed other medications/ interventions
Placebo-controlled trials		
Loratadine		
Grimfeld et al 2004 International (51 centers) Preventia I Study (Fair)	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 20. 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			
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 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Adverse events	Total withdrawals; withdrawals due to adverse events
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 overload	71 withdrawn from treatment phase; 102 total withdrew from both phases. Withdrawals due to AEs: 1 from placebo

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Study design Setting	Population Eligibility 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).
Milgrom 2007	Double-blind, randomized, placebo-controlled, parallel-group, multicenter (30)	Diagnosis of AR was supported by previous medical history and 1 or more of the following physical signs: clear nasal discharge, swelling and/or changes in color of turbinates, or cobblestoning (ie, dimpled appearance).

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Exclusion criteria	Age Gender Race/ethnicity
Placebo-controlled trials		
Fexofenadine		
Graft 2001 Meltzer 2004 (Fair)	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;	mean age: 9.1y, range 5-12 % male: 59 86% Caucasian 9% Black Weight: 36 kg (11), range 18-93
Milgrom 2007	Clinically relevant abnormalities or medical conditions that could interfere with the study (eg, severe asthma, bronchiolitis, wheezing, acute viral upper respiratory tract infection, vasomotor rhinitis, acute otitis media, or craniofacial abnormalities). Children receiving allergen immunotherapy were excluded if they required a change in the dose or frequency of injections; vaccinations within 2 weeks or planned vaccinations, received an investigational drug within 30 days before the study, or concomitantly used antihistamines, oral decongestants or adrenergic agonists, eye drops, systemic corticosteroids, nasal corticosteroids, or other sinus and allergy or cold remedies	Mean age 3.6 yrs 53% male 81% white 10% black 0.4% Asian 8% multiracial

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Interventions	Allowed other medications/ interventions
Placebo-controlled trials		
Fexofenadine		
Graft 2001 Meltzer 2004 (Fair)	F1: fexofenadine 15mg bid F2: fexofenadine 30 mg bid F3: fexofenadine 60mg bid P: placebo	NR
Milgrom 2007	Twice-daily fexofenadine hydrochloride, 30 mg, vs. placebo Average duration placebo 13.7 days (range, 1–17 days) and fexofenadine 14.2 days (range, 3–17 days).	Stable allergen immunotherapy

Evidence Table 20. 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
Milgrom 2007	Laboratory testing (blood chemistry and hematology profiles), physical examination, 12-lead electrocardiography, and vital signs (oral temperature, blood pressure, heart rate, and respiratory rate) and AE reporting	NR/NR/453 randomized	95/NR/453

Evidence Table 20. Adverse events in studies reporting safety outcomes in children

Author Year Country (Quality score)	Adverse events	Total withdrawals; withdrawals due to 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)	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
Milgrom 2007	Placebo vs. Fexofenadine N(%) Total 116 (50.2) vs. 111 (50.0) Respiratory system 40 (17.3) vs. 45 (20.3) Cough increased 7 (3.0) vs. 10 (4.5) Upper respiratory tract infection 16 (6.9) vs. 9 (4.1) Rhinitis 6 (2.6) vs. 9 (4.1) Pharyngitis 2 (0.9) vs. 6 (2.7) Asthma 8 (3.5) vs. 3 (1.4) Body as a whole 47 (20.3) vs. 38 (17.1) Fever 13 (5.6) vs. 13 (5.9) Accidental injury 7 (3.0) vs. 10 (4.5) Infection 14 (6.1) vs. 8 (3.6) Digestive system 30 (13.0) vs. 35 (15.8) Vomiting 11 (4.8) vs. 11 (5.0) Gastrointestinal pain 6 (2.6) vs. 6 (2.7) Diarrhea 7 (3.0) vs. 5 (2.3) Nervous system 11 (4.8) vs. 14 (6.3) Headache 9 (3.9) vs. 7 (3.2) Special senses 13 (5.6) vs. 13 (5.9) Otitis media 3 (1.3) vs. 8 (3.6) Ear pain 6 (2.6) vs. 3 (1.4)	NR; NR

Evidence Table 21. 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?
Head-to-head trials					
Delgado 1998 Brazil	Method NR	NR	Cetirizine group significantly older than terfenadine and astemizole groups.	yes	NR
Placebo-controlled trials					
Bloom 2004 USA 6-11y arm	Method NR	NR	Yes	Yes	States "double blind" but no details
Bloom 2004 USA 2-5y arm	Method NR	NR	Yes	Yes	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

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis
Head-to-head trials					
Delgado 1998 Brazil	NR	NR	NR	NR	unclear- no mention of withdrawals
Placebo-controlled trials					
Bloom 2004 USA 6-11y arm	States "double blind" but no details	Yes	states "no major deviations from subject compliance" appears to be no attrition	no	Yes
Bloom 2004 USA 2-5y arm	States "double blind" but no details	Yes	states "no major deviations from subject compliance" appears to be no attrition	no	Yes
Graft 2001	States "double blind" but no details	Yes	Attrition yes, others no	No	No; 38/875 were not evaluated for safety

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Post-randomization exclusions	Funding	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Head-to-head trials					
Delgado 1998 Brazil	none reported	Conselho Nacional de Pesquisa Brazil.	Yes	Not clear: "ECG was performed using standard techniques"	Unable to determine.
Placebo-controlled trials					
Bloom 2004 USA 6-11y arm	No	Schering-Plough	Yes	Yes	not clear if blinded.
Bloom 2004 USA 2-5y arm	No	Schering-Plough	Yes	Yes	not clear if blinded.
Graft 2001	No	Aventis Pharmaceuticals	Yes	Yes	Unclear if blinded

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Adequate duration of follow-up?	Quality score
Head-to-head trials		
Delgado 1998 Brazil	Yes (14 days)	Poor
Placebo-controlled trials		
Bloom 2004 USA 6-11y arm	15 days	Fair
Bloom 2004 USA 2-5y arm	15 days	Fair
Graft 2001	Yes (2 weeks)	Fair

Evidence Table 21. 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?
Milgrom 2007	NR	NR	Yes	Yes	Yes
Prenner 2006 USA, Latin America, S. Africa	Method NR	"central randomization service"	Yes	Yes	States "double blind" but no details
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
Simons 2003 US and Canada	Method NR	NR	Yes	yes	States "double blind" but no details

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis
Milgrom 2007	Yes	Yes	Yes/No/No/No	More withdrew from placebo group (17.3% vs 9.5%)	NR
Prenner 2006 USA, Latin America, S. Africa	States "double blind" but no details	Yes	Attrition and adherence: yes Crossover and contamination: no	No	No Unclear: data shown for 248/255 for cardiac safety
Salmun 2000 USA	States "double blind" but no details	Yes	No	Unclear	Unable to determine
Simons 2003 US and Canada	States "double blind" but no details	yes	Attrition yes, others no (89.4% completed)	No	Not clear for ECG, yes for other adverse events.

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Post-randomization exclusions	Funding	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Milgrom 2007	NR	Sanofi-Aventis	Yes	No	Unclear
Prenner 2006 USA, Latin America, S. Africa	No	Schering-Plough	Yes	Yes	Unclear if blinded
Salmun 2000 USA	NR	Schering-Plough	Yes	Yes	Not clear.
Simons 2003 US and Canada	No	Pfizer	Yes	Yes	Yes

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Adequate duration of follow-up?	Quality score
Milgrom 2007	No 2 weeks	Fair
Prenner 2006 USA, Latin America, S. Africa	15 days	Fair
Salmun 2000 USA	yes	Poor- unable to determine number enrolled, analyzed, withdrawn, because of ambiguous language, "121 children were enrolled and completed the multiple-dose tolerability study."
Simons 2003 US and Canada	? (7 days)	Fair

Evidence Table 21. 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?
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
Observational studies					
Rossi 2004 Time series	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)

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis
Winder 1996	States "double blind" but no details	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).
Observational studies					
Rossi 2004 Time series	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)

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Post-randomization exclusions	Funding	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Winder 1996	No	Pfizer	Yes- ECG	Yes	Yes
Observational studies					
Rossi 2004 Time series	Not applicable (NA)	NR	No	No	Unclear
Zuberbier 1996 adults and peds Case series	Not applicable (NA)	NR	No	No	Unclear

Evidence Table 21. Quality assessment of studies reporting safety outcomes in children

Author Year Country	Adequate duration of follow-up?	Quality score
Winder 1996	yes	Fair
Observational studies		
Rossi 2004 Time series	yes (4 weeks)	Poor: no details on AE ascertainment or reporting
Zuberbier 1996 adults and peds Case series	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

Evidence Table 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Study design Setting	Population Eligibility criteria	Exclusion criteria
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.

Evidence Table 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Age Gender Race/ethnicity	Interventions	Allowed other medications/ interventions
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)	17.0 months (SD4.1) 62.1% male Race/ethnicity NR	A: cetirizine oral solution 0.50 mg (0.25 mg twice daily) B: 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

Evidence Table 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	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)	(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	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 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Safety results	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)	Serious adverse events (cetirizine vs placebo) 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 (cetirizine vs placebo) 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 cetirizine, 47 placebo (p=0.189) Most common reasons for hospitalization were infection-related events without asthma (12 cetirizine vs 18 placebo) or injury, surgery, or procedure (8 cetirizine vs 15 placebo) 2 cetirizine and 8 placebo 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: cetirizine: 14.82 kg (SD 1.89) placebo: 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.	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 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Study design Setting	Population Eligibility criteria	Exclusion criteria
Simons 2007 Early Prevention of Asthma in Atopic Children (EPAAC) 10 European countries, Australia, and South Africa.	Randomized, double-masked, parallel-group, placebo-controlled, multi-center	Age 12–24 months, had atopic dermatitis, elevated specific IgE to either grass pollen or house dust mite, and a family history of allergy.	Asthma or any other systemic disease; height or body mass were below the 5th percentile; any severe neurologic or psychologic disorder requiring medical treatment; intolerant of levocetirizine or any other piperazine antihistamine, or to the parabens used as preservatives in H1-antihistamine liquid formulations; a personal history or sibling history of sleep apnea; or renal insufficiency or any metabolic condition that might affect the elimination of levocetirizine.

Evidence Table 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Age Gender Race/ethnicity	Interventions	Allowed other medications/ interventions
Simons 2007 Early Prevention of Asthma in Atopic Children (EPAAC) 10 European countries, Australia, and South Africa.	Mean age 19.35 months 62.6% male	Levocetirizine 0.125 mg/kg or placebo twice daily for 18 months.	NR

Evidence Table 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Method of outcome assessment and timing of assessment	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Efficacy results
Simons 2007 Early Prevention of Asthma in Atopic Children (EPAAC) 10 European countries, Australia, and South Africa.	Adverse events captured by spontaneous reporting on the diary cards, and by asking the child's caregiver, at each scheduled visit, "Did you notice anything unusual about the child's health since the last visit?" Preventing or delaying asthma and the efficacy of levocetirizine in preventing urticaria - to be published in another publication	NR/NR/510	75/NR/510	NR

Evidence Table 22. Placebo-controlled trials in children with atopic dermatitis

Author Year Country (Quality rating)	Safety results	Adverse events: behavioral, cognitive, psychomotor development
Simons 2007 Early Prevention of Asthma in Atopic Children (EPAAC) 10 European countries, Australia, and South Africa.	Levocetirizine vs. Placebo One or more adverse events 247 (96.9%) vs. 244 (95.7%) Treatment-attributed adverse events 13 (5.1%) vs. 16 (6.3%) Serious adverse events 31 (12.2%) vs. 37 (14.5%) Treatment-attributed serious adverse events 0 vs. 1 (0.4%)* Adverse events that led to discontinuation (treatment–emergent) 5 (2.0%) vs. 3 (1.2%) Wheezing 12 (4.7%) vs. 19 (7.5%) Dermatitis, atopic 3 (1.2%) vs. 6 (2.4%) Gastroenteritis 2 (0.8%) vs. 5 (2.0%) Cough 4 (1.6%) vs. 2 (0.8%) Bronchopneumonia 4 (1.6%) vs. 1 (0.4%) Febrile convulsion 4 (1.6%) vs. 0 Urticaria 1 (0.4%) vs. 3 (1.2%) Bronchitis, chronic 0 vs. 3 (1.2%) Pneumonia 2 (0.8%) vs. 0 Abnormal behavior 2 (0.8%) vs. 3 (1.2%) Aggression 0 vs. 1 (0.4%) Agitation 1 (0.4%) vs. 0 Anxiety 0 vs. 1 (0.4%) Burning sensation 0 vs. 1 (0.4%) Convulsions 1 (0.4%) vs. 0 Epilepsy 1 (0.4%) vs. 0 Febrile convulsions 5 (2.0%) vs. 1 (0.4%) Headache 1 (0.4%) vs. 4 (1.6%) Insomnia 3 (1.2%) vs. 2 (0.8%) Irritability 0 vs. 4 (1.6%) Nervousness 1 (0.4%) vs. 0 Nightmare 0 vs. 1 (0.4%) Sleep disorder 1 (0.4%) vs. 1 (0.4%) Somnolence 0 vs. 1 (0.4%) Syncope 0 vs. 1 (0.4%)	Levocetirizine vs. Placebo Median (range) Gross motor development Sit alone 6 (6–7) vs. 6 (6–8) Crawl 8 (7–10) vs. 8 (7–10) Stand alone 10 (9–12) vs. 10 (9–12) Walk alone 12 (11–14) vs. 12 (11–14) Climb stairs with assistance 14 (12–16) vs. 14 (13–17) Climb stairs without assistance 17 (14–20) vs. 18 (15–20) Run 16 (14–18) vs. 16 (14–19) Fine motor development Pincer (2-finger) grip 10 (8–13) vs. 11 (7–14) Pencil (3-finger) grip 17 (12–21) vs. 18 (12–21) Match cubes (build 4 block tower) 18 (14–20) vs. 18 (14–20) Show hand preference 17 (12–23) vs. 18 (12–22) Speech and language Pronounce first five words 14 (12–18) vs. 15 (12–18) Name many objects 18 (15–22) vs. 18 (16–22) Pronounce short sentences 22 (19–25) vs. 23 (20–25)

Evidence Table 23. Quality assessment of placebo-controlled trials in children with atopic dermatitis

	Internal validity					
Author Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Simons 2007	Unclear	NR	NR	Yes	Unclear, "stated as double-blind"	Unclear, "stated as double-blind"
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

Evidence Table 23. Quality assessment of placebo-controlled trials in children with atopic dermatitis

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
Simons 2007	Yes	Yes, No, No, No	No/No 85.9% completed in levocetirizine group 84.3% completed in placebo group	Yes	No
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	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

Evidence Table 23. Quality assessment of placebo-controlled trials in children with atopic dermatitis

			External validity			
Author Year Country	**Funding**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Run-in/ washout**	**Class naïve patients only**	**Control group standard of care**
Simons 2007	NR	Poor	NR/NR/510	Patients had to discontinue H1 antihistamines prior to enrollment	NR	Yes
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	UCB, S.A. (Brussels, Belgium).	Fair	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 24. Trials of 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 24. Trials of 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

Evidence Table 25. Systematic review

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)

Evidence Table 25. Systematic review

	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?**
Bender 2003	Yes	N/A	Yes	Yes	Yes	Yes

Evidence Table 25. Systematic review

		External Validity					
Author, Year	**Adequate duration of follow-up?**	**Adequate description of population?**	**Groups similar at baseline?**	**# screened / eligible / enrolled?**	**Exclusion criteria specified?**	**Funding**	**Overall Quality**
Bender 2003	Yes	Yes	Yes	Yes, # studies	Yes	NR	Fair