

Drug Class Review on Newer Antihistamines

Update #2: Preliminary Scan Report #3

July 2009

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

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

April 2006 (searches through August 2005)

Date of Last Update Scans

Scan #2, May 2008

Scan #1, May 2007

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients.

Key Questions

1. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?
2. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in harms?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one newer antihistamine is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adult or pediatric outpatients with the following indications:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Urticaria

Interventions

Cetirizine hydrochloride (Zyrtec, Reactine)

Loratadine (Claritin)
Fexofenadine hydrochloride (Allegra)
Desloratadine (Clarinex)

Effectiveness outcomes

- Symptom alleviation (e.g., nasal congestion, rhinorrhoea, sneezing, itching and pain from skin irritations, etc.)
- Functional capacity (e.g., physical, social and occupational functioning, quality of life, etc.)
- Time to relief of symptoms (e.g., time to onset, duration of relief)
- Duration of effectiveness (e.g., switch rate)

Harms outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events
- Specific adverse events or withdrawals due to specific adverse events (e.g., CNS effects, sedation, GI effects, dry mouth, urinary retention, etc.)

Study designs

1. For effectiveness, controlled clinical trials and systematic reviews
2. For harms, controlled clinical trials and observational studies

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations from March 2007 to June 23, 2009 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote v X2[®]) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 76 citations. Of these, there are 19 potentially relevant trials that included levocetirizine, a recently approved drug. Table 1 summarizes the populations and comparisons included in these studies. Titles and abstracts for these citations are also available in Appendix A. Note, there are also 15 potentially relevant trials identified from the previous scan in May 2008. Table 2 summarizes these studies.

Table 1. New potentially relevant trials (N=19)

Study	N, duration	Population	Comparison	Focus
Bachert 2004 (XPert trial?)	551, 4 weeks for primary endpoint, 6 months for secondary	Adults with persistent allergic rhinitis	Levocetirizine 5 mg vs. placebo	Primary endpoint: symptom score, quality of life Secondary endpoint:
Ciebiada 2006	20, 6 weeks (cross-over)	Adults with persistent allergic rhinitis	Montelukast 10 mg vs. desloratadine 5 mg vs. levocetirizine 5 mg vs. montelukast+ desloratadine vs. montelukast+ levocetirizine vs. placebo	Nasal symptom score
Ciprandi 2004	30, 2 weeks	Adults with seasonal allergic rhinitis	Before and after treatment with levocetirizine 5 mg vs. desloratadine 5 mg vs. placebo	Total symptom score
Ciprandi 2005	30, 4 weeks	Adults with perennial allergic rhinitis	Desloratadine 5 mg vs. levocetirizine 5 mg vs. placebo	Nasal symptom relief, total symptom score
Ciprandi 2005	40, 4 weeks	Adults with persistent allergic rhinitis	Levocetirizine 5 mg vs. placebo	Nasal symptom relief, total symptom score
Day 2004	373, 2 days	Adults with seasonal allergic rhinitis	Levocetirizine 5 mg vs. desloratadine 5 mg vs. placebo	Major symptom complex score
Day 2008	418, 2 days	Adults with ragweed-induced seasonal allergic rhinitis	Levocetirizine 5 mg vs. montelukast 10 mg vs. placebo	Major symptom complex score
De Blic 2005	177, 6 weeks	Children with seasonal allergic rhinitis	Levocetirizine 5 mg vs. placebo	Total symptom score, nasal symptom relief, quality of life
Kapp 2006	NR, 4 weeks	Adults with chronic idiopathic urticaria	Levocetirizine 5 mg vs. placebo	Signs and symptom relief, quality of life, work productivity
Leynadier 2001	470, 2 weeks	Adults with seasonal allergic rhinitis	Levocetirizine 2.5 mg, 5 mg, 10 mg, vs. placebo	Total symptom score and relief
Mahmoud 2008	20, 4 weeks	Adults with seasonal allergic rhinitis	Levocetirizine (dose not reported in abstract) vs. placebo	Symptom relief and blood analysis of inflammatory cells
Nettis 2006	106, 6 weeks	Adults with chronic idiopathic urticaria	Levocetirizine 5 mg vs. placebo	Symptom relief, quality of life
Pasquali 2006	50, 8 weeks	Adults with persistent allergic rhinitis w/or w/out asthma	Levocetirizine vs. placebo	Diary cards, quality of life
Passalacqua 2004	23, 24 hours (cross-over)	Adults with allergic rhinitis	Desloratadine vs. levocetirizine	Wheal and flare measures, total symptom score, instant symptom score
Patel 2008	403, 2 days	Adults with seasonal allergic rhinitis due to ragweed	Levocetirizine 5 mg vs. montelukast 10 mg vs. placebo	Symptom relief and score
Potter 2005	306, 4 weeks	Children with perennial allergic rhinitis	Levocetirizine 5 mg vs. placebo	Symptom relief, quality of life
Potter 2009	886, 4 weeks	Adults with chronic idiopathic urticaria	Levocetirizine 5 mg vs. desloratadine 5 mg	Pruritus score, quality of life, global satisfaction
Stubner 2004	NR, 2 days	Adults with seasonal or perennial allergic rhinitis	Loratadine 10 mg vs. levocetirizine 5 mg	Major symptom complex and complex symptom score
Walter-Canonica 2006 (companion to XPert trial?)	551, 6 months	Adults with persistent allergic rhinitis	Levocetirizine 5 mg vs. placebo	Quality of life, health status

Table 2. Potentially relevant trials identified from previous scan #2 (N=15)

Study	N, duration	Population	Comparison	Focus
Enonmoto 2007	20, 5.5 hrs	Adults with cedar pollinosis	Cetirizine vs. placebo	Symptom scores
Grob 2008	137, 6 weeks	Adults with chronic idiopathic urticaria	Desloratadine 5 mg vs. placebo	QoL scores
Hampel 2007	393, 8 days	Children with allergic symptoms	Fexofenadine 15 or 30 mg vs. placebo	Treatment emergent adverse events (safety tolerability)
Ho 2007	120, 4 weeks	Adults with allergic rhinitis	Cetirizine 10 mg, zafirlukast 20 mg, cafirlukast 20 mg, cetirizine+ zafirlukast, placebo	Nasal symptom score
Korsgren 2007	36, 12 days	Adults with grass pollen-sensitive allergies	Oral cetirizine 10 mg vs. topical cetirizine vs. placebo	Symptom relief and score
Kupczyk 2007	21, 5 days	Adults with atopy	Ranitidine 150 mg vs. loratadine 10 mg vs. placebo	Symptom relief and score
Kupczyk 2007	15, 5 days	Adults with atopy	Montelukast 10 mg vs. loratadine 10 mg vs. placebo	Symptom relief and score
Meltzer 2007	NR, 24 hrs	Adults and adolescents with histamine induced skin flares and wheals	Fexofenadine 10 mg vs. desloratadine 5 mg vs. placebo	Change in skin flares and wheals
Milgrom 2007	231, 2 weeks	Children with allergic rhinitis	Fexofenadine 30 mg BID vs. placebo	Safety and tolerability
Ortonne 2007	137, 6 weeks	Adults with chronic idiopathic urticaria	Desloratadine 5 mg vs. placebo	Change in pruritus severity and wheals, symptom score
Philip 2007	1365, 6 weeks	Adults and adolescents with perennial allergic rhinitis	Montelukast 10 mg vs. placebo vs. cetirizine 10 mg (2:2:1)	Symptom score
Pradalier 2007	NR, 2 weeks	Adults with seasonal allergic rhinitis	Desloratadine 5 mg vs. placebo	QoL, symptom relief
Simons 2007	510, 18 months	Children with atopy	Levocetirizine 0.125 mg/kg vs. placebo	Urticaria
Simons 2007	Same as above	Same as above	Same as above	Safety and tolerability
Spector 2007	NR, 4 weeks	Adults with chronic idiopathic urticaria	Fexofenadine 180 mg vs. placebo	Work productivity and QoL

New Drugs

We identified one newly approved drug, levocetirizine, a selective H1-receptor blocker, which is only available in the US.

Drug	Approval date	Indication
Levocetirizine (Xyzal)	5/25/2007	Season and perennial allergic rhinitis, chronic idiopathic urticaria

We found two other drugs that have publications and that have studies pending in Clinicaltrials.gov. These two drugs are bilastine and rupatadine which are not yet approved by the FDA or Health Canada.

New Indications

None.

New Safety Alerts

None.

Appendix A. Abstracts of potentially relevant trials of Newer Antihistamines (N=19)

Bachert, C., J. Bousquet, et al. (2004). "Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis." Journal of Allergy & Clinical Immunology **114**(4): 838-44.

BACKGROUND: Allergic Rhinitis and its Impact on Asthma in collaboration with the World Health Organization initiative reclassified allergic rhinitis, like asthma, by duration and severity. The Xyzal in Persistent Rhinitis Trial is the first large, long-term clinical trial studying patients with persistent rhinitis as defined by Allergic Rhinitis and its Impact on Asthma. **OBJECTIVES:** Two primary objectives were defined: comparison of the Rhinoconjunctivitis Quality of Life Questionnaire overall score and Total 5 Symptoms Score (rhinorrhea, sneezing, nasal congestion, and nasal and ocular pruritus) over a period of 4 weeks between levocetirizine 5 mg and placebo. Secondary endpoints included similar evaluations at 1 week and 3, 4.5, and 6 months, summary scores for a general health status questionnaire (Medical Outcomes Survey Short Form 36), a pharmacoeconomic assessment, comorbidities, and a safety evaluation. **METHODS:** The Xyzal in Persistent Rhinitis Trial was a 6-month double-blind, placebo-controlled, multicenter, multinational trial in 551 patients. Adults with persistent rhinitis sensitized to both grass pollen and house dust mite were randomized to receive levocetirizine 5 mg/d or placebo. **RESULTS:** A total of 421 patients completed the full study. Levocetirizine significantly improved both the Rhinoconjunctivitis Quality of Life Questionnaire overall score and the Total 5 Symptoms Score from week 1 to 6 months (all P values <.001). Medical Outcomes Survey Short Form 36 summary scores were also improved in the levocetirizine group compared with the placebo group. Treatment cessation because of lack of effect, comorbidities, and overall costs of disease, and comorbidities per working patient per month (160.27 vs 108.18) were lower in the levocetirizine group. **CONCLUSION:** Levocetirizine was shown to improve quality of life and symptoms and to decrease the overall costs of the disease over the 6-month treatment period.

Ciebiada, M., M. Gorska-Ciebiada, et al. (2006). "Montelukast with desloratadine or levocetirizine for the treatment of persistent allergic rhinitis." Annals of Allergy, Asthma, & Immunology **97**(5): 664-71.

BACKGROUND: Montelukast sodium is approved as a treatment for intermittent and persistent allergic rhinitis (AR), but it has not been evaluated as combined therapy with antihistamines for persistent AR. **OBJECTIVE:** To investigate the effects of 6 weeks of treatment of persistent AR with desloratadine, levocetirizine, or montelukast alone or in combination. **METHODS:** A randomized, double-blind, placebo-controlled crossover study was performed. Patients were assigned to 2 arms: 20 received montelukast, 10 mg/d, desloratadine, 5 mg/d, or both or placebo and 20 received montelukast, levocetirizine, or both, 5 mg/d, or placebo. The treatment periods were separated by 2-week washout periods. Symptom scoring, skin prick tests, spirometry, rhinometry, and nasal lavage were performed the day before and the last days of the treatment periods. Eosinophil cationic protein levels were evaluated by means of nasal lavage. **RESULTS:** The mean +/- SD total baseline nasal symptom score was 7.7 +/- 0.49 before treatment, 3.74 +/- 0.54 after desloratadine use, 3.6 +/- 0.48 after montelukast use, and 3.04 +/- 0.4 after montelukast-desloratadine use. The mean +/- SD baseline nasal symptom score was

7.95 +/- 0.68 before treatment, 3.02 +/- 0.64 after levocetirizine use, 3.44 +/- 0.55 after montelukast use, and 2.14 +/- 0.39 after montelukast-levocetirizine use. The greatest improvement in nasal symptoms occurred after combination treatment. Decreases in the level of eosinophil cationic protein were greater after the combined use of montelukast and antihistamine than after each agent given alone. **CONCLUSIONS:** For persistent AR, the combination of montelukast and either desloratadine or levocetirizine is more effective than monotherapy with these agents.

Ciprandi, G., I. Cirillo, et al. (2005). "Desloratadine and levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with perennial allergic rhinitis: a pilot study." International Immunopharmacology **5**(13-14): 1800-8.

BACKGROUND: Nasal obstruction is the main symptom in patients with perennial allergic rhinitis. Some new antihistamines have been demonstrated to be capable of improving this symptom. **OBJECTIVE:** The aim of this pilot study was to evaluate nasal symptoms, nasal airflow, eosinophils, and IL-4 in patients with perennial allergic rhinitis, before and after treatment with two new antihistamines: desloratadine and levocetirizine. **METHODS:** Thirty patients with perennial allergic rhinitis were evaluated, 26 males and 4 females (mean age 26+/-7.1 years). All of them received either desloratadine (5 mg/daily) or levocetirizine (5 mg/daily) or placebo for 4 weeks. The study was double-blind, parallel-group, placebo-controlled, and randomized. Total symptom score (including: rhinorrhea, nasal itching, sneezing, and nasal obstruction) was assessed before and after treatment. Rhinomanometry and decongestion test, nasal lavage, and nasal scraping were performed in all subjects before and after treatment. Eosinophils were counted by conventional staining; IL-4 was measured by immunoassay of fluids recovered from nasal lavage. **RESULTS:** Desloratadine and levocetirizine treatment induced significant symptom relief and significant reduction of IL-4. Both antihistamines significantly affected all parameters in comparison with placebo. **CONCLUSIONS:** This pilot study demonstrates the effectiveness of antihistaminic treatment in: i) relieving nasal symptoms, including obstruction, ii) improving nasal airflow, iii) exerting decongestant activity, iv) reducing eosinophil infiltration, and v) diminishing IL-4 levels.

Ciprandi, G., I. Cirillo, et al. (2004). "Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study." Clinical & Experimental Allergy **34**(6): 958-64.

BACKGROUND: Allergic rhinitis is characterized by an IgE-dependent inflammation. Nasal obstruction is related to allergic inflammation. Some antihistamines have been demonstrated to be capable of improving this nasal symptom. **OBJECTIVE:** The aim of this pilot study was to evaluate nasal symptoms, nasal airflow, inflammatory cells, and cytokine pattern in patients with seasonal allergic rhinitis (SAR), before and after treatment with levocetirizine, desloratadine, or placebo. **METHODS:** Thirty patients with SAR were evaluated, 27 males and three females (mean age 26.9+/-5.4 years). All of them received levocetirizine (5 mg/day), desloratadine (5 mg/day), or placebo for 2 weeks. The study was double-blind, parallel-group, placebo-controlled, and randomized. Total symptom score (TSS) (including: rhinorrhea, nasal itching, sneezing, and nasal obstruction) was assessed before and after treatment. Rhinomanometry, nasal lavage, and nasal scraping were performed in all subjects before and after treatment. Inflammatory cells were counted by conventional staining; IL-4 and IL-8 were measured by

immunoassay on fluids recovered from nasal lavage. RESULTS: Levocetirizine treatment induced significant symptom relief ($P=0.0009$) and improved nasal airflow ($P=0.038$). Desloratadine also relieved TSS ($P=0.01$), but did not affect nasal airflow. Levocetirizine significantly reduced eosinophils ($P=0.029$), neutrophils ($P=0.005$), IL-4 ($P=0.041$), and IL-8 ($P=0.02$), whereas desloratadine diminished IL-4 only ($P=0.044$). Placebo treatment did not significantly affect any evaluated parameters. CONCLUSIONS: This pilot study demonstrates the effectiveness of levocetirizine in: (i) relieving nasal symptoms, (ii) improving nasal airflow, (iii) reducing leucocyte infiltration, and (iv) diminishing cytokine levels. These findings are the first evidence of the effectiveness of levocetirizine in SAR.

Ciprandi, G., I. G. Cirillo, et al. (2005). "Levocetirizine improves nasal symptoms and airflow in patients with persistent allergic rhinitis: a pilot study." European Annals of Allergy & Clinical Immunology **37**(1): 25-9.

BACKGROUND: Nasal obstruction is the main symptom in patients with persistent allergic rhinitis. Some antihistamines have been demonstrated to be capable of improving this symptom. The aim of this pilot study was to evaluate nasal symptoms, nasal airflow, and decongestant activity in patients with persistent allergic rhinitis, before and after treatment with levocetirizine or placebo. METHODS: Forty patients with persistent allergic rhinitis were evaluated, 35 males and 5 females (mean age 23.3 +/- 5.9 years). All of them received levocetirizine (5 mg/daily) or placebo for 4 weeks. The study was double-blind, parallel-group, placebo-controlled, and randomized. Total symptom score (including: nasal itching, sneezing, rhinorrhea, and nasal obstruction) was assessed before and after treatment. Rhinomanometry and decongestion test were performed in all subjects before and after treatment. RESULTS: Levocetirizine treatment induced: significant symptom relief ($p<0.001$), improved nasal airflow ($p<0.001$), reduction of reversibility percentage ($p<0.05$), and increase of total airflow after decongestion test ($p<0.03$). Placebo did not improve nasal symptoms and airflow. CONCLUSIONS: This pilot study demonstrates the effectiveness of levocetirizine in: i) relieving nasal symptoms, including obstruction, ii) improving nasal airflow, and iii) exerting decongestant activity. Thus, these findings are the first evidence of the impact on airflow and the decongestant activity exerted by levocetirizine in persistent allergic rhinitis.

Day, J. H., M. P. Briscoe, et al. (2004). "Comparative clinical efficacy, onset and duration of action of levocetirizine and desloratadine for symptoms of seasonal allergic rhinitis in subjects evaluated in the Environmental Exposure Unit (EEU)." International Journal of Clinical Practice **58**(2): 109-18.

The Environmental Exposure Unit, an indoor pollen challenge system to test anti-allergic medications, was used to compare the onset and duration of action and the efficacy of levocetirizine and desloratadine, two recently developed H1-antagonists. In this double-blind, placebo-controlled, parallel-group study, qualified subjects were randomised to once-daily levocetirizine 5 mg ($n = 141$), desloratadine 5 mg ($n = 140$) or placebo ($n = 92$) and exposed to ragweed pollen on two consecutive days (7 h and 6 h). Symptoms were self-rated every 30 min. On both days, levocetirizine produced a greater improvement in the major symptom complex score (primary efficacy variable) than desloratadine ($p = 0.015$); both were better than placebo ($p < 0.001$). Levocetirizine acted earlier (1 h vs. 3 h) and produced greater symptom relief at 24 h than desloratadine ($p =$

0.003). Levocetirizine also alleviated nasal obstruction better than desloratadine ($p = 0.007$) on day 1; and better than placebo ($p = 0.014$) after the second dose on day 2, which was not observed with desloratadine. Levocetirizine and desloratadine were safe and well tolerated.

Day, J. H., M. P. Briscoe, et al. (2008). "Efficacy of levocetirizine compared with montelukast in subjects with ragweed-induced seasonal allergic rhinitis in the Environmental Exposure Unit." *Allergy & Asthma Proceedings* **29**(3): 304-12.

Levocetirizine dihydrochloride, a potent H1-receptor antagonist, and montelukast sodium, a selective leukotriene receptor antagonist, have been approved for the treatment of seasonal allergic rhinitis (SAR), but target two different pathways that cause SAR symptoms. The study objective was to compare the efficacy of levocetirizine (LCTZ), 5 mg, and montelukast (MLKT), 10 mg, in reducing SAR symptoms in ragweed-sensitive adults exposed to ragweed pollen in the Environmental Exposure Unit (EEU). This randomized, double-blind, placebo-controlled, parallel-group study of 418 adult subjects with SAR to ragweed compared the efficacy of LCTZ, MLKT, and placebo administered once daily (11:00 A.M.) for 2 consecutive days in the EEU. There were three evaluation periods: period I, 0-5 hours after first dose; period II, 22.5-24 hours after first dose; and period III, 0-4.5 hours after second dose. The primary efficacy variable was the Major Symptom Complex (MSC) score (six symptoms) over period I. Both active drugs significantly improved the MSC score compared with placebo in all periods. The adjusted mean MSC score difference between LCTZ and MLKT was -0.93 ($p = 0.100$) in period I, -3.11 ($p < 0.001$) in period II, -2.42 ($p < 0.001$) in period III, and -1.88 ($p < 0.001$) over the total treatment period. The same trends were observed for the Total Symptom Complex score (10 symptoms) and most individual symptoms. Subject-reported global satisfaction was greater for LCTZ compared with MLKT and placebo. All treatments had a favorable safety profile. LCTZ, 5 mg, was more effective than MLKT, 10 mg, in subjects with SAR and had better subject-reported global satisfaction.

de Blic, J., U. Wahn, et al. (2005). "Levocetirizine in children: evidenced efficacy and safety in a 6-week randomized seasonal allergic rhinitis trial." *Pediatric Allergy & Immunology* **16**(3): 267-75.

Studies evaluating newer antihistamines in children are few. Levocetirizine is a potent and highly selective H1-antihistamine with a proven efficacy in adults. Primary objective was to assess the efficacy of levocetirizine 5 mg once-daily in reducing seasonal allergic rhinitis (SAR) symptoms, as measured by Total Four Symptom Score (T4SS = sum of sneezing, rhinorrhea, nasal and ocular pruritus), over the first 2 wk of treatment. Efficacy over 4 and 6 wk of treatment, effect on nasal congestion and on health-related quality of life as measured by PRQLQ (Paediatric Rhinoconjunctivitis Quality of Life Questionnaire) were among the major secondary objectives. A double-blind, randomized, placebo-controlled study including 177 children with a documented SAR (to grass and/or weed) for at least a year and having a mean baseline T4SS $> \text{or} = 6$ (out of 12). Children evaluated daily the severity of T4SS and nasal congestion on a scale from 0 (absent) to 3 (severe). PRQLQ responses were assessed on a scale from 0 (not bothered) to 6 (extremely bothered) and analysed descriptively. Global evaluation of disease evolution judged by investigators, parents and children was made on a scale from 1 (marked worsening) to 7 (marked improvement). For the primary objective, levocetirizine was

statistically highly superior to placebo with a difference in adjusted means of 1.29 (95% CI: 0.66-1.92) in favour of levocetirizine ($p < 0.001$). The effect of levocetirizine was almost twice that of placebo (94.1% relative improvement over placebo). Nasal congestion was improved with levocetirizine reaching maximum difference to placebo of 0.31 ($p < 0.05$), a relative improvement over placebo of 77.5%. PRQLQ scores at week 2 improved with levocetirizine more than with placebo (0.85 vs. 0.51, respectively) remaining larger after 4 and 6 wk of treatment. In the study, 84.3%, 80.9%, 80.9% of children had their disease evolution rated as slightly-to-markedly improved by, respectively, the investigators, the parents and children themselves. Incidence of treatment-emergent adverse events was similar in both groups (33.7% with levocetirizine; 30.7% with placebo). No child in the levocetirizine group discontinued treatment because of adverse events. The 6-wk duration of this study was longer than the usual 2-4-wk duration for similar studies and shows that levocetirizine controls SAR symptoms in children over the entire pollen season. Copyright 2005 Blackwell Munksgaard

Kapp, A. and W. J. Pichler (2006). "Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study." *International Journal of Dermatology* **45**(4): 469-74.

BACKGROUND: Chronic idiopathic urticaria (CIU) is defined by the almost daily presence of urticaria for at least 6 weeks without an identifiable cause. Symptoms include short-lived wheals, itching, and erythema. CIU impedes significantly a patient's quality of life (QoL). Levocetirizine is an antihistamine from the latest generation approved for CIU. **AIM:** To investigate the efficacy of levocetirizine, 5 mg, and placebo for the symptoms and signs of CIU, as well as for the QoL and productivity. **METHODS:** The primary criteria of evaluation were the pruritus severity scores over 1 week of treatment and over 4 weeks. The QoL was assessed via the Dermatology Life Quality Index (DLQI). **RESULTS:** Baseline pruritus severity scores were comparable in the two treatment groups (2.06 \pm 0.58). After 1 week, levocetirizine was superior to placebo and demonstrated a considerable efficacy (difference=0.78, $P < 0.001$). This efficacy was maintained over the entire study period (4 weeks, $P < 0.001$). The number and size of wheals were considerably reduced compared with placebo over 1 week and over the total treatment period ($P \leq 0.001$). This was paralleled by an improvement in the QoL (DLQI: 7.3 units in the levocetirizine group and 2.4 units in the placebo group) and a higher productivity at work in the levocetirizine group (3.0 workdays lost per patient per month in the placebo group, 0.3 in the levocetirizine group). No unexpected adverse events occurred. **CONCLUSIONS:** Levocetirizine, 5 mg once daily, is an effective treatment for CIU, characterized not only by a rapid and sustained response, but also by an important improvement in QoL.

Leynadier, F., K. Mees, et al. (2001). "Efficacy and safety of levocetirizine in seasonal allergic rhinitis." *Acta Oto-Rhino-Laryngologica Belgica* **55**(4): 305-12.

OBJECTIVE: Pharmacodynamic studies have demonstrated that levocetirizine is the active enantiomer of cetirizine. This first therapeutic trial of levocetirizine aimed at determining the dosage with the best benefit/risk ratio in patients with seasonal allergic rhinitis (SAR). **METHODS:** Patients with seasonal allergic rhinitis were randomised in a placebo-controlled, double-blind, parallel-group multicentre study 2.5, 5, 10 mg levocetirizine or placebo once daily during 2 weeks. Patients filled in a diary evaluation

card every evening before taking study medication using the classical (0-3) scale for assessment of severity of sneezing, rhinorrhea, nasal congestion, nasal pruritus and ocular pruritus over the preceding 24 hours. The Total Four-Symptom Score (T4SS) was calculated by adding the individual symptom scores, excluding nasal congestion. RESULTS: 470 patients were included and constituted the intent-to-treat population. All 3 doses of levocetirizine were significantly superior to placebo in reducing the mean T4SS over the 2 weeks (all P (0.001). Additionally, individual symptom severity scores for sneezing, rhinorrhea, itchy nose, and itchy eyes were also significantly decreased for all doses of levocetirizine. Levocetirizine was significantly superior to placebo in reducing symptom severity with an important global treatment effect (P = 0.0001), except for nasal congestion. Furthermore, there was simple linear relationship between levocetirizine dosages and reduction of T4SS (P = 0.001). All doses were well tolerated, somnolence was higher with 10 mg (10.2%) than 5 mg (1.7%) and other adverse events were more frequent with the highest dose. CONCLUSION: Levocetirizine 5 mg once daily has an optimal benefit/risk ratio in the treatment of SAR.

Mahmoud, F., N. Arifhodzic, et al. (2008). "Levocetirizine modulates lymphocyte activation in patients with allergic rhinitis." Journal of Pharmacological Sciences **108**(2): 149-56.

Levocetirizine, a second generation non-sedating antihistamine that blocks the H(1) histamine receptor, may exhibit immunoregulatory properties that augment its primary pharmacological mechanism. To investigate this possibility, 13 Kuwaiti seasonal allergic rhinitis (SAR) patients were treated with levocetirizine for four weeks in comparison with a 7-member placebo-treated control group, followed by clinical evaluation and flow cytometric analysis of peripheral venous blood for inflammatory cell and lymphocyte subpopulation profiles. Relative to the controls, levocetirizine-treated patients exhibited an expected reduction in early phase allergic symptoms, including 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). Levocetirizine treatment also correlated with a significant increase in the percentage of CD4+CD25+ T cells (P<0.001). The ability of levocetirizine to reduce percentage representation of cell phenotypes known to contribute to inflammatory tissue damage (eosinophils, CD4+CD29+, CD4+CD212+, and CD4+CD54+) and expand percentages of CD4+CD25+, which may include protective immunoregulatory (Treg) cells, indicates that the drug has pharmacological potential beyond the immediate effects of H(1) histamine-receptor inhibition. Although the present data does not define a therapeutic mechanism, the results reported here establish important trends that may be used to guide future mechanistic examination of immunoregulatory capacity of H(1) inhibitors.

Nettis, E., M. C. Colanardi, et al. (2006). "Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study." British Journal of Dermatology **154**(3): 533-8.

BACKGROUND: Chronic urticaria is a common skin condition. It is frequently a disabling disease because of the persistence of clinical symptoms, the unpredictable course and its negative influence on the quality of life. OBJECTIVES: To determine whether levocetirizine is efficacious in the treatment of chronic idiopathic urticaria. METHODS: A randomized, double-blind, placebo-controlled study was conducted in

106 patients with a diagnosis of chronic idiopathic urticaria. A 1-week single blind placebo run-in period (baseline) was followed by a 6-week double blind active treatment period. The patients were randomized to receive one of the following treatments once daily: (a) oral levocetirizine 5 mg, or (b) oral placebo. The study ended after another 1-week single blind placebo washout period. **RESULTS:** The evaluable population consisted of 100 patients. Levocetirizine administered once daily is effective and well tolerated in the treatment of the symptoms of chronic idiopathic urticaria and in improving the patient's quality of life. Levocetirizine was superior to placebo in reducing the mean total symptoms score as well as individual symptoms, the number of daily episodes and the number of weals, the overall severity of symptoms and the quality of life. The significant beneficial effects of levocetirizine lasted only during the active trial, while at follow-up there was a significant worsening of all the variables evaluated in this study, after the end of the active trial (week 7). **CONCLUSIONS:** A global assessment indicates that levocetirizine 5 mg once daily is an effective agent in patients with chronic idiopathic urticaria, as its action provides a rapid and satisfactory control of the symptoms and measures of subjective disease, although this is limited to the duration of treatment.

Pasquali, M., I. Baiardini, et al. (2006). "Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters." Clinical & Experimental Allergy **36**(9): 1161-7.

Background Levocetirizine (LCZ) has been shown to be effective in allergic rhinitis. We evaluated its clinical efficacy, anti-inflammatory actions and its effects on quality of life (QoL) with a specific instrument in the asthma-rhinitis comorbidity. Methods Fifty adult patients with persistent rhinitis with/without asthma were enrolled. After a 1-week run-in for baseline evaluation, they were randomized to LCZ or placebo for 8 weeks. Cromolyn and salbutamol were permitted on demand. Rhinoconjunctivitis and asthma symptoms were evaluated by diary cards. QoL was assessed by the specific Rhinasthma questionnaire and the generic SF-36 at different time-points. Nasal scrapings and lavages were also performed for inflammatory cell count and mediator assessment. Results Ten patients dropped out for unrelated reasons and the remaining completed the study with no side-effect. Symptoms began to decrease in the active group at the second week of treatment when the difference with the placebo group became significant (0.05) and so remained until the end of the trial. Starting from 2 weeks of therapy, there was a significant decrease vs. baseline in all the four components of the Rhinasthma questionnaire only in the active group. The intergroup comparison became significant ($P < 0.05$) at 4 weeks. The SF-36 detected only sporadic differences between groups. Eosinophils and neutrophils in nasal scraping were significantly decreased in the LCZ group vs. baseline at all times. Nasal mediators were under the detection limits and no analysis could be performed. In the active group, only two patients used rescue medications compared with 13 patients in the placebo group. Conclusions LCZ is clinically effective and capable of improving the rhinitis-asthma-related QoL.

Passalacqua, G., L. Guerra, et al. (2004). "Comparison of the effects in the nose and skin of a single dose of desloratadine and levocetirizine over 24 hours." International Archives of Allergy & Immunology **135**(2): 143-7.

BACKGROUND: Desloratadine (DL) and levocetirizine (LCZ) are the newest

commercialized antihistamines. Pharmacokinetics, pharmacodynamics and clinical data are available for both drugs, but there is to date no direct comparison involving the nose and skin at the same time. We compared the effects of a single dose of the two drugs in the nose and skin over 24 h. **METHODS:** Twenty-three patients with symptomatic allergic rhinitis were enrolled in a randomized double-blind crossover administration of DL and LCZ. The histamine-induced wheal and flare was measured at baseline and 2 and 24 h after dosing. A reflective total symptom score (rTSS) for the previous 24 h was assessed before and after each dose. An instant symptom score was also measured at various time points after each drug. **RESULTS:** LCZ provided greater inhibition of the flare at 2 h ($p = 0.05$) and at 24 h ($p = 0.007$) and greater inhibition of the wheal only at 2 h ($p = 0.02$). The decrease in wheal and flare was significant versus baseline ($p = 0.007$) with both drugs. The rTSS of the previous 24 h decreased significantly with both LCZ (11.53 vs. 8.0; $p < 0.05$) and DL (11.3 vs. 7.9; $p < 0.05$). The instant TSS progressively decreased in parallel with both drugs, but a difference in favor of LCZ was seen 2 h after dosing. **CONCLUSIONS:** Single doses of DL and LCZ had a comparable effect on nasal symptoms, but LCZ was faster and displayed a greater effect on histamine wheal.

Patel, P. and D. Patel (2008). "Efficacy comparison of levocetirizine vs montelukast in ragweed sensitized patients." Annals of Allergy, Asthma, & Immunology **101**(3): 287-94.

BACKGROUND: To date, no adequate data are available on direct comparison of the efficacy of levocetirizine, a recently approved histamine₁-antihistamine, with that of a leukotriene antagonist in the treatment of seasonal allergic rhinitis (SAR) symptoms. **OBJECTIVE:** To compare the efficacy of therapeutic doses of 5 mg of levocetirizine and 10 mg of montelukast in ragweed sensitized patients. **METHODS:** A randomized, double-blind, placebo-controlled, parallel-group study was conducted between July and October 2006. Symptomatic patients with SAR were exposed to ragweed pollen under controlled conditions in an environmental exposure chamber for 4 to 5 hours after treatment with 5 mg of levocetirizine, 10 mg of montelukast, or matched placebo on 2 consecutive days. The mean change from baseline in pollen-induced rhinitis symptoms, expressed as a major symptoms complex (MSC) score (sum of scores for rhinorrhea, itchy nose, sniffles, nose blows, sneezes, and watery eyes), in period 1 (first 5 hours after first drug intake) was the primary efficacy outcome. **RESULTS:** A total of 611 patients were screened, of whom 403 were randomized to receive treatment (102 placebo, 152 levocetirizine, and 149 montelukast). The MSC score in period 1 was progressively decreased to a significantly greater extent in the levocetirizine group compared with the montelukast and placebo groups (adjusted mean differences, -2.18 [95% confidence interval, -3.35 to -1.01; $P < .001$] and -2.22 [95% confidence interval, -3.51 to -0.92; $P < .001$] for levocetirizine vs montelukast and vs placebo, respectively). The effect of 10 mg of montelukast was not significantly different compared with placebo. Levocetirizine also achieved a significantly faster onset of action within 2.5 hours of administration. Both products were well tolerated. **CONCLUSIONS:** This study in an environmental exposure chamber confirms the therapeutic efficacy of 5 mg of levocetirizine in improving symptoms of SAR, which was superior to 10 mg of montelukast.

Potter, P. C. and G. Paediatric Levocetirizine Study (2005). "Efficacy and safety of levocetirizine on symptoms and health-related quality of life of children with perennial allergic rhinitis: a double-blind, placebo-controlled randomized clinical trial." Annals of Allergy, Asthma, &

Immunology **95**(2): 175-80.

BACKGROUND: This randomized study examined the efficacy and safety of levocetirizine in pediatric patients with perennial allergic rhinitis. Health-related quality of life (HRQL) was also investigated, which is particularly relevant in children because of the effects of rhinitis on learning, social activities, and comorbidity. **OBJECTIVE:** To evaluate the effect of levocetirizine on the Total 4 Symptoms Score, the 50% response rate, the Pediatric Rhinitis Quality of Life Questionnaire (PRQLQ), and investigators' global evaluation of symptom improvement. **METHODS:** Double-blind, placebo-controlled, randomized, multicenter trial of levocetirizine, 5 mg once daily for 4 weeks, in 306 children with perennial allergic rhinitis aged 6 to 12 years. There were 154 children in the levocetirizine arm and 152 in the placebo group who completed daily diary cards, and the PRQLQ and investigators' global evaluations were conducted at 3 visits. **RESULTS:** The levocetirizine group showed a significant improvement in 2-week and 4-week Total 4 Symptoms Score compared with placebo ($P = .001$ and $P = .008$, respectively). The 50% response rate for the first 2 weeks was 12.3% for the levocetirizine group compared with 3.9% for the placebo group ($P = .01$). The investigators' global evaluation also favored levocetirizine, because 57.1% of the children in the levocetirizine group were considered markedly or moderately improved compared with 44.7% in the placebo group. Levocetirizine also provided a significantly greater HRQL improvement than placebo at 2 weeks ($P = .01$), and the frequency of adverse events did not differ significantly from those seen in the placebo group. **CONCLUSION:** The study confirmed the efficacy of levocetirizine in relieving symptoms of perennial allergic rhinitis in children between 6 and 12 years of age. A HRQL benefit greater than placebo was shown. The treatment was well tolerated.

Potter, P. C., A. Kapp, et al. (2009). "Comparison of the efficacy of levocetirizine 5 mg and desloratadine 5 mg in chronic idiopathic urticaria patients." Allergy **64**(4): 596-604.

BACKGROUND: Nonsedating H(1)-antihistamines are recommended for the treatment of urticaria by the recent EAACI/GA(2)LEN/EDF guidelines. The aim of this study was to compare the efficacy, after 4 weeks of treatment, with levocetirizine 5 mg and desloratadine 5 mg, both once daily in the morning, in symptomatic chronic idiopathic urticaria (CIU) patients. **METHODS:** This multi-center, randomized, double-blind study involved 886 patients (438 on levocetirizine and 448 on desloratadine). The primary objective was to compare their efficacy on the mean pruritus severity score after 1 week of treatment. 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, were secondary efficacy measures. **RESULTS:** Levocetirizine led to a significantly greater decrease in pruritus severity than desloratadine over the first treatment week; mean pruritus severity scores of 1.02 and 1.18 for levocetirizine and desloratadine, respectively ($P < 0.001$). The result was similar for the entire 4-week treatment period ($P = 0.004$). In addition, levocetirizine decreased pruritus duration and the mean CIU composite scores to a significantly greater extent than desloratadine during the first week ($P = 0.002$ and 0.005 , respectively) and over the entire study ($P = 0.009$ and $P < 0.05$, respectively). Similarly, levocetirizine increased the patients' global satisfaction after one and 4 weeks ($P = 0.012$ and 0.021 , respectively), compared with desloratadine. Safety and tolerability were similar in both groups. **CONCLUSIONS:**

Levocetirizine 5 mg was significantly more efficacious than desloratadine 5 mg in the treatment of CIU symptoms.

Stubner, P., R. Ziegelmayer, et al. (2004). "A direct comparison of the efficacy of antihistamines in SAR and PAR: randomised, placebo-controlled studies with levocetirizine and loratadine using an environmental exposure unit - the Vienna Challenge Chamber (VCC)." Current Medical Research & Opinion **20**(6): 891-902.

OBJECTIVE: The Vienna Challenge Chamber (VCC) is an established method for the controlled exposure of patients to specific allergens, used to make valid comparisons between antihistamines. The aim of the significantly more than loratadine at all time two placebo-controlled, randomised studies reported here was to compare the efficacy and safety of levocetirizine 5 mg od and loratadine 10 mg od in subjects suffering from seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR). Subjects and methods: During each study period, SAR and PAR subjects were exposed to grass pollen or house-dust mite allergens, respectively for 6 h on 2 consecutive days in the VCC. Each day, medications were administered 2 h after the start of the challenge; with a washout of at least 5 days between each period. The main criterion for evaluation of efficacy was the major symptom complex (MSC) for SAR and the complex symptom score (CSS) for PAR. **RESULTS:** The pattern of patients' response was similar in SAR and PAR. Both levocetirizine and loratadine were superior to placebo in alleviating SAR and PAR symptoms at all time intervals evaluated during the two study days. Levocetirizine decreased the mean MSC score intervals in SAR subjects, with the most marked difference observed on day 2 ($p = 0.002$). In PAR patients, although with borderline significance ($p = 0.08$), levocetirizine decreased the mean CSS more than loratadine. Levocetirizine appeared to have a faster onset of action than loratadine in SAR (45 min versus 1 h 15 min) and PAR (1 h versus 1 h 30 min). However, these apparent differences were not tested for statistical significance. Both medications were well tolerated and no treatment-related adverse events were reported. This level of antihistamine efficacy was maintained regardless of whether the subjects' rhinitis was seasonal or perennial. **CONCLUSION:** This study demonstrated that levocetirizine is superior to loratadine in improving symptoms in SAR and that there is a similar trend in PAR.

Walter Canonica, G., J. Bousquet, et al. (2006). "Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis." Respiratory Medicine **100**(10): 1706-15.

BACKGROUND: Allergic rhinitis is a chronic respiratory disorder with a detrimental impact on health-related quality of life (HRQOL) and health status. Enhancement and maintenance of patient function and well-being are therefore considered as essential. **OBJECTIVE:** To determine whether long-term treatment with levocetirizine 5mg improves HRQOL and health status in persistent allergic rhinitis (PER) patients assessed with RQLQ and SF-36 scales over a 6-month period. **METHODS:** The Xyzal in PER Trial (XPRT) was a multi-center, double-blind, parallel-group study. A total of 551 patients were randomized to receive levocetirizine 5mg or placebo once daily for 6 months and assessed for symptoms, HRQOL (Rhinoconjunctivitis Quality of Life Questionnaire: RQLQ) and health status (SF-36). Sensitivity of the RQLQ and SF-36 to disease severity was tested to ensure their suitability for use in PER patients. Treatment effect was assessed by means of repeated measures analyses. **RESULTS:** Over the 6-month treatment period, levocetirizine showed statistically significant improvements over

placebo in HRQOL ($P < 0.001$ for all RQLQ domains and overall scores) and health status ($P < \text{or} = 0.004$ for SF-36 physical and mental summary scores; $P < 0.05$ for all SF-36 scales). The relative improvement of levocetirizine over placebo exceeded the predefined clinically meaningful threshold of 30% for all RQLQ scores and the improvement from baseline was 3 times the established MID for RQLQ. **CONCLUSION:** The RQLQ and SF-36 could be used to measure HRQOL and health status in PER patients. Long-term treatment with levocetirizine provides sustained improvement of HRQOL and reduces disease burden in PER patients.