

## Levocetirizine: Review of its Use in the Treatment of Seasonal Allergic Rhinitis

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### Abstract

**Background:** Levocetirizine (LCZ), the active R-enantiomer of cetirizine, is a second-generation antihistamine approved for symptom treatment due to seasonal allergic rhinitis (SAR), perennial allergic rhinitis, and chronic idiopathic urticaria in patients  $\geq 6$  months of age.

**Objective:** To review available literature about pharmacokinetics, pharmacodynamics, efficacy, tolerability, quality of life, and pharmacoeconomics of LCZ use in adults and children with SAR.

**Methods:** Databases searched were: MEDLINE, CINAHL Plus with Full Text, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, EMBASE, NHS Economic Evaluation Database, and Database of Abstracts of Reviews of Effectiveness. Search terms included levocetirizine, histamine H<sub>1</sub> antagonists—non-sedating, seasonal allergic rhinitis, pregnancy, quality of life, case reports, cost, and pharmacoeconomics. Relevant article reference lists were also used to obtain additional articles.

**Results:** LCZ exhibits rapid and extensive absorption, high affinity/selectivity for H<sub>1</sub> receptor, and rapid onset and long duration of action. Eight articles assessing clinical efficacy were reviewed. In 4 placebo-controlled studies, LCZ 5 mg/day significantly reduced nasal symptoms in 3 studies and had similar efficacy in 1 study. LCZ was more effective in reducing SAR symptoms vs. desloratadine 5 mg/day but not vs. rupatadine (RUP) 10 mg/day, and RUP was more effective than LCZ in reducing nasal symptoms ( $P = 0.02$ ). Addition of LCZ 5 mg/day to fluticasone nasal spray therapy improved nasal blockage symptoms only ( $P < 0.005$ ). Studies investigating anti-inflammatory effects produced inconsistent results. LCZ was not associated with serious adverse events and is generally well tolerated with complaints of somnolence and fatigue; also, there was an increase in febrile seizures in infants.

**Conclusion:** LCZ is an effective and well-tolerated second-generation antihistamine used for the treatment of SAR in adults and children, but its effects on inflammatory markers and performance versus other treatment options require further investigation.

**Keywords:** levocetirizine, allergic rhinitis, antihistamine, pharmacokinetics, quality of life, pharmacoeconomic

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## Introduction

Atopic disease, such as allergic rhinitis (AR), is a major cause of morbidity in children and adults in the industrialized world, affecting quality of life, productivity at work or school and social activities.<sup>1,2</sup> Epidemiological estimates of AR range from 19% to 30%.<sup>3,4</sup> The incidence and lifetime prevalence of AR appears to be on the rise around the world, perhaps due to increased recognition and diagnosis.<sup>5</sup>

AR occurs due to IgE-mediated inflammation of the nose after allergen exposure. Attributable allergens include pollen, mold, grasses, house dust mites, animal dander, and indoor and outdoor pollution.<sup>1</sup> The 2008 update of Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines divide allergic rhinitis into two classifications: intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER). Patients who suffer from IAR have symptoms <four days/week or less than four consecutive weeks, and PER symptoms are present for <four days/week and more than four consecutive weeks. These two classifications are considered more reflective of clinical practice and are not synonymous with previously used classifications of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and occupational allergic rhinitis. Both SAR and PAR are classified based on time of exposure to allergen.<sup>1</sup> SAR is usually caused by seasonal outdoor allergens (eg, pollens, molds) as opposed to PAR which is thought to be due to non-seasonal presence of indoor allergens (eg, house dust mites, animal dander).<sup>1</sup> Published clinical studies describing effects of pharmacological agents on AR use the older method of classification. Suspected cases of AR can be confirmed by skin prick test (SPT) containing standard allergens or by measurement of serum allergens-specific IgE in cases difficult to diagnose.<sup>1,6</sup> Patients present with nasal itching, sneezing, rhinorrhea, and nasal obstruction, but smell disturbances, ocular involvement, and headache can also be seen.<sup>6</sup>

The severity of AR can be categorized as mild vs. moderate/severe. Mild AR is characterized by nasal and/or ocular symptoms that do not affect regular sleep and ability to engage in normal daily activities. Patients are classified as having moderate/severe AR if  $\geq$ one of following are present: sleep disturbance, troublesome symptoms, or impairment of daily activities, school or work.<sup>1</sup> The interaction between genetics and environmental factors increases risk of

development of AR. However, potential risk factors for AR related to pregnancy (eg, low birth weight, maternal age, multiple gestation), early-life exposure to allergens, and ethnicity require further study to be understood.<sup>1</sup>

Treatments for AR include oral and intranasal antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, and allergen-specific immunotherapy. Oral H<sub>1</sub> antihistamines are first-line treatment for mild and moderate/severe IAR and mild PER. First-line therapy for management of moderate/severe PER is intranasal corticosteroids.<sup>1</sup>

Levocetirizine (Xyzal<sup>®</sup>) is a second-generation antihistamine approved for relief of symptoms due to SAR or PAR and for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in patients  $\geq$ 6 months of age.<sup>7</sup> Levocetirizine (LCZ) is a member of piperazine class and active R-enantiomer of cetirizine (CET). LCZ, a H<sub>1</sub> receptor antagonist, could also be defined as inverse agonist that binds to H<sub>1</sub> histamine receptor while in its inactive form stabilizing receptor and decreasing histamine release.<sup>8</sup> The purpose of this article is to review published literature about efficacy and tolerability of LCZ in patients with SAR. Additionally, pharmacokinetics, dynamics, economics and quality of life studies will be discussed.

## Methods

The following databases were used to assemble appropriate articles for this review: Biomedical Reference Collection: Comprehensive, MEDLINE, CINAHL Plus with Full Text, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Methodology Register, EMBASE, International Pharmaceutical Abstracts, Nursing and Allied Health: Comprehensive, NHS Economic Evaluation Database, and Database of Abstracts of Reviews of Effectiveness. Search terms included levocetirizine, histamine H<sub>1</sub> antagonists—non-sedating, seasonal allergic rhinitis, pregnancy, quality of life, case reports, cost, and pharmacoeconomics. Relevant article reference lists were used to obtain additional articles. English-language articles characterizing efficacy, tolerability, pharmacodynamics, pharmacokinetics, quality of life (QOL), and pharmacoeconomics of LCZ were reviewed.



## Pathophysiology of Seasonal Allergic Disease

AR is an IgE-mediated response to common environmental substances.<sup>1</sup> During initial exposure, allergens (eg, food, medications, pollen) are engulfed and displayed by epithelial cells, including nasal airway dendritic and B cells.<sup>9</sup> During this first exposure to allergen, or sensitization, naïve CD4+ cells differentiate into allergen-specific CD4+/CD25+ cells.<sup>10</sup> These T-cells produce cytokines including IL-3, IL-4, IL-5, and IL-9, which act to attract eosinophils and basophils cells to area and perpetuate production of IgE through B cell isotype switching.<sup>9</sup>

Immunologic course of subsequent allergen exposures can then be divided into early- and late-phase responses. During another exposure, dendritic cells present offending allergens to corresponding high-affinity IgE receptors on surface of mast cells.<sup>11</sup> Thirty minutes later, an early-phase response occurs, releasing preformed mediators, mainly histamine, and newly synthesized mediators (prostaglandins and leukotrienes).<sup>10</sup> Mast cell involvement, in which preformed histamine is released from storage granules, is characterized by increased vascular permeability, initiation of itch and sneezing sensations, and glandular secretion resulting in sneezing, itching, and rhinorrhea.<sup>10</sup> Late-phase response occurs ~six hours post-allergen exposure, and is characterized by recruitment of eosinophils, basophils, and T-cells to nasal mucosa, which acts to extend pro-inflammatory state initiated by mast cells.<sup>9,10</sup>

## Levocetirizine Pharmacokinetics

Cetirizine is a racemate of two enantiomers, LCZ and dextrocetirizine, and LCZ is the active R-enantiomer.<sup>12</sup> These enantiomers are configurationally stable and undergo no interconversion.<sup>12,13</sup> Compared with dextrocetirizine, LCZ has a longer half-life, lower total body clearance, lower renal clearance and smaller volume of distribution ( $V_D$ ).<sup>7,13</sup>

## Absorption

Based on a pharmacokinetic study by Strolin Benedetti et al of four healthy volunteers, LCZ was rapidly and extensively absorbed, with a mean (SD)  $t_{max}$  0.75 (0.5) hours and 98.3% of a 5 mg radiolabelled dose recovered in urine (85.4%) and feces (12.9%) at 168 hours.<sup>12</sup>

## Distribution

LCZ has a low  $V_D$  (0.3–0.4 L/kg), which allows plasma concentrations high enough to bind with  $H_1$  receptors preventing histamine release without being widely available enough to increase likelihood of drug-drug interactions or accumulation in heart and liver causing dose-dependent side effects.<sup>13–15</sup> Plasma protein binding is 91%.<sup>16</sup>

## Metabolism

Metabolism appears to be a minor means of elimination. Thirteen metabolites have been identified, comprising 2.4% of a 5 mg dose at 48 hours.<sup>12</sup> Metabolism-based drug interactions are not likely as non-renal clearance of LCZ is 9.7 mL/min.<sup>13</sup> Because LCZ is not extensively metabolized, intersubject variability of pharmacokinetic parameters is unlikely.<sup>17</sup> LCZ does not appear to undergo extensive first-pass metabolism based on mean (SD) clearance (Cl/F) of 44.38 (17.72 mL/min) [0.57 (0.18 mL/min/kg)], which is much lower than hepatic blood flow at 21 mL/min/kg.<sup>12</sup> In a study by Baltes et al, 12 healthy males and 12 healthy females were administered [<sup>14</sup>C]-LCZ 10 mg and mean AUC was 4072.5 h·ng/mL (2828.6–5654.1 h·ng/mL) with a low coefficient of variance of 17.8%.<sup>13</sup>

## Excretion

Elimination appears to occur primarily by excretion in kidneys through glomerular filtration and tubular secretion.<sup>12,14</sup> Renal clearance is 31.98 mL/min and tubular secretion is 23.1 mL/min, with 94% excreted in urine.<sup>14</sup> Additionally, the unbound fraction is 0.074.<sup>14</sup> The plasma half-life ( $t_{1/2}$ ) of LCZ tablets and solution is between 8 and 9 hours.<sup>7</sup>

## Pharmacodynamics

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients (n = 373) with SAR who were exposed to ragweed in an Environmental Exposure Unit (EEU) and given either LCZ 5 mg, desloratadine (DSL) 5 mg or placebo (PLA).<sup>18</sup> Measurements of efficacy included major symptoms complex (MSC) defined as runny nose, sniffles, itchy nose, nose blows, sneezes, and watery eyes, and total symptom score (TSC) composed of MSC plus itchy eyes/ears, itchy throat,



cough, and post-nasal drip. Determination of MSC and TSC occurred at three time-points, which were averages of half-hour increments measured post-medication administration (period 1: 0–5 hours, period 2: 22.5–24 hours post-dose, and period 3: 24–28.5 hours). Onset of action of LCZ was observed at one hour, compared to three hours with DSL and duration of action of 24 hours for both agents. Baseline MSC scores were similar for all groups [mean (SD), LCZ 14.86 (5.5); DSL 16.04 (6.05); PLA 15.84 (5.58)]. At period 1, the difference in MSC between LCZ and PLA was  $-3.68$  [95% CI  $-4.95$ ,  $-2.41$ ,  $P < 0.001$ ] and the difference between DSL and PLA was  $-1.81$  [95% CI  $-3.08$ ,  $-0.54$ ,  $P < 0.001$ ], in favor of active agent groups. The difference in MSC between LCZ and DSL at period 1 was  $-1.87$  [95% CI  $-3.00$ ,  $-0.73$ ,  $P = 0.001$ ] in favor of LCZ. LCZ was superior to PLA based on TSC at all time-points ( $P \leq 0.001$ ) and DSL at periods 1 and 3 ( $P = 0.003$ ,  $P = 0.017$  respectively).<sup>18</sup>

A randomized, double-blind, placebo-controlled, parallel study of efficacy exposing patients ( $n = 403$ ) with SAR to ragweed was conducted utilizing an Environmental Exposure Chamber (EEC). Patients were given either LCZ 5 mg, montelukast (MLK) 10 mg, or PLA for two consecutive days.<sup>19</sup> Primary endpoint was MSC at end of period 1 (five hours post-drug administration). The decrease in MSC at period 1 was significant for LCZ vs. MLK and PLA with an adjusted mean difference of  $-2.18$  [95% CI  $-3.35$ ,  $-1.01$ ],  $P < 0.001$  and  $-2.22$  [95% CI  $-3.51$ ,  $-0.92$ ],  $P < 0.001$ , respectively. No difference was seen between MLK and PLA at period 1 ( $-0.03$  [95% CI  $-1.34$ ,  $1.27$ ],  $P = 0.96$ ), and thus no onset of action was able to be determined for MLK in this study.<sup>19</sup>

Passalacqua et al conducted a randomized, controlled, double-blind, two-way crossover study of a single dose of LCZ 5 mg or DSL 5 mg measuring wheal-and-flare responses in symptomatic AR patients ( $n = 23$ ).<sup>20</sup> A histamine HCL 0.1% solution was administered to forearms inducing wheal-and-flare responses, and to grade reflective total symptom scores (rTSS) and instant TSS scores (iTSS). The rTSS consisted of sneezing, itching, rhinorrhea, obstruction, and ocular redness/itching, and iTSS were patient symptoms scores of rTSS at 20 min, 40 min and 1, 2, 4, 6, 8, and 12 hours post-drug administration. Significant

differences in flare reactions were observed between LCZ and DSL at 2 ( $P = 0.05$ ) and 24 hours ( $P = 0.007$ ). Differences in improvement of wheal diameter were seen between LCZ and DSL only at 2 hours ( $P = 0.02$ ). No difference in baseline mean (SD) rTSS occurred at baseline between two active groups [LCZ 11.53 (2.2), DSL 11.3 (2.5)]. A difference in rTSS from baseline was seen at 24 hours for LCZ [11.53 (2.2) vs. 8.0 (2.0),  $P < 0.05$ ] and DSL [11.3 (2.5) vs. 7.9 (2.4),  $P < 0.05$ ]. A significant difference in iTSS was observed between LCZ and DSL only at 2 hours ( $P = 0.01$ ), in favor of LCZ.<sup>20</sup>

### Receptor affinity and selectivity

Four distinct histamine receptors have been identified thus far ( $H_1$ ,  $H_2$ ,  $H_3$ , and  $H_4$  receptors), and LCZ binds with high affinity to  $H_1$  receptor ( $K_i = 2$  nM).<sup>21,22</sup> LCZ binds with twice the affinity to  $H_1$  receptors as cetirizine, and with 30-times more affinity than the S-enantiomer. LCZ dissociates from  $H_1$  receptors much slower than the S-enantiomer (dissociation half-times of 142 minutes vs. 6 minutes).<sup>23</sup> This high affinity and slow dissociation time contributes to effectiveness and long duration of action of LCZ.<sup>24</sup> Additionally, because inflammatory environments can become acidic and most pharmacokinetic studies are conducted at a pH of 7.4, Gillard et al conducted a study of LCZ during a pH decrease from 7.4 to 5.8 and found a 3-fold increase in affinity to  $H_1$  receptors (4.1 to 1.5 nM).<sup>25</sup>

Due to low selectivity for  $H_1$  receptors and similar confirmation of histaminic and muscarinic receptors, first-generation antihistamines (eg, diphenhydramine, hydroxyzine) are associated with anti-cholinergic effects including dry mouth, urinary retention and blurry vision.<sup>24</sup> The combination of high binding selectivity of LCZ for  $H_1$  receptors and a  $H_1$ /muscarinic receptor binding selectivity ratio of  $>20,000$  reduces likelihood of anti-cholinergic side effects.<sup>22</sup>

### Immunologic effects

Because histamine is one of many mediators involved in allergic reaction, blocking only histamine may not alleviate all symptoms of AR.<sup>26–28</sup> Anti-inflammatory properties, such as effects on eosinophils and T-cells, have been investigated as additional benefit of medications used to treat AR.<sup>29,30</sup> However, some debate exists about LCZ's anti-inflammatory



properties. In an *in vitro* study of lipopolysaccharide-stimulated eosinophils, LCZ influenced eosinophil production of inflammatory mediators, but did not induce apoptosis of isolated human eosinophils.<sup>31</sup>

In Mahmoud et al,<sup>32</sup> patients ( $n = 20$ ) were given LCZ 5 mg/daily or PLA for 4 weeks. Treatment with LCZ or PLA did not lead to reduction in concentration of lymphocyte major populations (CD3+, CD4+, CD8+, CD19+, and CD16+CD56+). For those randomized to LCZ, significant decrease in percentage of CD4+CD29+, CD4+CD212+, CD4+CD54+, and ICAM-1 (LCZ vs. baseline,  $P < 0.05$ ) was seen along with significant increase in CD4+CD25+ ( $P < 0.001$ ). LCZ did not significantly effect CD4+CD45RO+ or CD4+CD45RA+ concentrations. No significant change in any of cell populations occurred in PLA group.<sup>32</sup>

In a study of patients ( $n = 30$ ) with SAR given LCZ 5 mg/day,<sup>33</sup> DSL 5 mg/day or PLA for 2 weeks, IL-4 levels were reduced by both LCZ and DSL vs. baseline ( $P = 0.041$  and  $P = 0.044$ ) while only LCZ reduced IL-8 levels when compared to baseline ( $P = 0.02$ ). LCZ was found to reduce eosinophil counts compared with DSL and PLA ( $P = 0.008$ ,  $P = 0.0002$ ), and DSL also reduced eosinophil counts compared with PLA ( $P = 0.0007$ ). Neutrophil counts were reduced by LCZ in comparison with PLA as well ( $P = 0.00009$ ).

### Special populations

Complexities with enrollment and medication dispensing, data collection, and symptom reporting in pediatric populations have led to limited number of AR studies in this population.<sup>34,35</sup> However, children may have different dosing requirements than adults based on physiological development and changes in drug distribution during maturation. In prospective pharmacokinetic study of cetirizine 0.25 mg/kg twice daily use in children 14–46 months and weight range 8.2–20.5 kg, assessments of LCZ concentrations showed body-weight increased Cl/F by 0.44 L/h/kg.<sup>36</sup> Additional study using LCZ 0.125 mg/kg twice daily in children with mean (SD) age 20.7 (3.7) months and mean (SD) weight 11.6 (1.8) kg reported elimination half-life 4.1 (0.7) hours and clearance 1.05 mL/min/kg.<sup>37</sup> There is increased clearance of LCZ in this age group, possibly requiring higher milligram per kilogram dose and more frequent dosing, as opposed to traditional

once-daily dosing, to treat symptoms of AR.<sup>36,37</sup> In children 6–12 years, pharmacokinetic study of LCZ showed mean (SD) elimination half-life 5.7 (0.2) hours and  $V_D$  0.4 (0.02 L/kg), supporting once-daily dosing in this age range.<sup>38</sup>

LCZ is classified as FDA pregnancy category B based primarily on data collected for cetirizine as no large well-controlled studies using LCZ are available.<sup>7</sup> First-generation antihistamines, specifically chlorpheniramine and tripelemnamine, are antihistamines-of-choice based on supportive animal and human data.<sup>39</sup> Second-generation antihistamines with reassuring animal studies (ie, cetirizine and loratadine) are recommended for use after chlorpheniramine or tripelemnamine, ideally after first trimester.<sup>39</sup> Use of LCZ by nursing mothers is not recommended based on data collected on cetirizine indicating low birth weight in mice and presence in breast milk.<sup>7</sup>

### Efficacy and Quality of Life

Efficacy and QOL assessment tools used in clinical studies are described on Table 1.<sup>33,40–50</sup>

deBlic et al<sup>40</sup> conducted a 6-week, randomized, multicenter, double-blind, placebo-controlled study in 41 centers in France and Germany in 177 children (66.1% males; 90.4% Caucasian; age range 6–13 years). The objective was to evaluate effect of LCZ 5 mg daily on T4SS in first two weeks of treatment. Secondary variables included efficacy over 4 and 6 weeks of treatment, nasal congestion, PRQLQ, and global evaluation of illness evolution with Likert scale (1 = worsening and 7 = improvement) given by patient's parent/guardian and investigator. Study eligibility included confirmed and documented SAR (grass and/or weed pollen) for  $\geq 1$  year, history of AR, pollen sensitization and symptoms when being evaluated for inclusion. Patients with asthma were included if they were using short-acting  $B_2$ -agonists only as needed. Nasal sodium cromoglicate spray was allowed as rescue medication from visit 3 onwards.

Mean (SD) T4SS values for LCZ vs. PLA groups at baseline were 7.64 (1.4) vs. 7.67 (1.73), respectively. Patients randomized to LCZ group reported statistically significant improvement from baseline in mean T4SS over weeks 1, 2, 4, and 6 ( $P < 0.001$ ) and vs. PLA over weeks 2, 4, and 6 ( $P < 0.001$ ). Those receiving LCZ had significant improvement in

**Table 1.** Description of the assessments used in efficacy and quality of life studies.<sup>33,40–50,57</sup>

- Each of the following rhinoconjunctival symptom is graded on 4-point scale (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) with scores ranging from 0–15.
  - Total 5 Symptom Score (T5SS: sneezing, rhinorrhea, nasal pruritus, ocular pruritus, and nasal congestion)
  - Total 4 Symptom Score (T4SS: sneezing, rhinorrhea, nasal pruritus, and ocular pruritus)
  - Total Symptom Score (TSS: rhinorrhea, nasal itching, sneezing, and nasal obstruction)
  - Total Nasal Score (TNS: sneezing, runny nose, nasal itching, nasal congestion)
  - Total Nasal Symptom Score (TNSS: of sneezing, rhinorrhea, nasal itching, nasal congestion, and postnasal drip)
- QOL assessment tools
  - Juniper Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)
    - RQLQ contains 7 domains (emotional function, eye symptoms, non-hay fever symptoms, nasal symptoms, practical problems, and sleep problems) with 28 items scored on 7-point scale (0 = not troubled/none of the time to 6 = extremely troubled/all the time)
  - mini-RQLQ
    - Mini-RQLQ scores similar to RQLQ, but covers 5 domains (activities, practical problems, nose symptoms, eye symptoms, and other symptoms) with total of 14 items
  - Pediatric Rhinoconjunctivitis Quality-of-Life Questionnaire (PRQLQ)
    - PRQLQ (validated age range 6–12 years) contains 5 domains (23 items) which include nasal symptoms, ocular symptoms, other symptoms, practical problems, and activity limitations also scored similar to RQLQ
  - Work Productivity and Activity Impairment-Allergy Specific (WPAI-AS) questionnaire
    - WPAI is a quantitative measure of health outcomes focusing on the effects of general health and symptom severity on work productivity and regular activity. WPAI scores are measured as percentages of scheduled work hours actually worked and productivity, along with a set of questions assessing impairment in regular daily activities (other than work). Severity of symptoms are scaled (1 = all of the time, 6 = none of the time) with higher scores correlating with less interference. By multiplying the severity score by number of days the symptoms occurred, the overall score (0 to 35) would describe severity (higher score = less severity).
  - Epworth Sleepiness Scale (ESS)
    - The ESS asks patients how likely they are to doze off or fall asleep in eight different situations. Situations include: sitting and reading; watching television; sitting (inactive in a public place); passenger in a car for an hour without a break; lying down to rest in the afternoon when circumstances permit; sitting and talking to someone; sitting quietly after lunch without alcohol; in a car, while stopped for a few minutes in traffic. Patients rate symptom severity on a scale (0 = never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing) to determine level of daytime sleepiness. A score of  $\geq 16$  indicates a high level of daytime sleepiness.
- Addiction Research Center Inventory 49 (ARCI-49) questionnaire is a shortened version of ARCI. ARCI relates to alterations in activity/sedation, motivation, mood/perception changes and physiological processes induced by psychoactive medications. ARCI-49 is comprised of 49 questions (to be answered yes-no) and relates to 5 different factors (euphoria, dysphoria, sedation, intellectual efficacy/energy, and activation) in order to differentiate between changes in mood caused by psychoactive drugs

sneezing, rhinorrhea, and nasal pruritus over 6 weeks compared with PLA ( $P < 0.004$ ) but not for ocular pruritus; also, LCZ relieved nasal congestion significantly from PLA only at week 3 ( $P < 0.05$ ).

Those in LCZ group showed larger (but not statistically significant) improvement in PRQLQ domains at weeks 4 and 6 and overall scores at weeks 2, 4 and 6 (Table 2). However, baseline PRQLQ scores were not provided, making assessment of any change from baseline difficult. In first two weeks, investigators rated improvement in children's disease evolution at 84.3% for LCZ and 54.5% for PLA. Over 50% of treated children, children's parent/guardian, and investigators rated moderate-to-marked improvement of global evaluation of illness evolution consistently

better for LCZ. Treatment-emergent adverse events (TEAE) occurred in 33.7% vs. 30.7% of patients in LCZ vs. PLA groups. Commonly reported adverse events (AEs) included headache, bronchitis, and epistaxis and one child from PLA group discontinued study due to AE. Thirty-two patients did not complete study and it was unclear why these patients left. Authors report discontinuation due to lack of efficacy which occurred two times more frequently in PLA group vs. LCZ group.

Leynadier et al<sup>41</sup> conducted a 2-week, Phase II, pharmacodynamic, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in France and Germany in 470 patients (50% males; age ranging 17–72 years). The objective was to determine dosage

**Table 2.** Percent improvement in quality of life scores after two weeks of treatment with levocetirizine versus placebo in children and adults.

	deBlic et al <sup>40*</sup> PRQLQ			Segall et al <sup>43</sup> RQLQ	
	LCZ 5 mg (n = 89)	PLA (n = 88)		LCZ 5 mg (n = 285)	PLA (n = 293)
Baseline	*	*	Baseline	3.43 (1.15) <sup>€</sup>	3.35 (1.08) <sup>€</sup>
Nose symptoms	30.9%	15.7%	Nasal symptoms <sup>£</sup>	36.3%	28.9%
Eye symptoms	40.6%	23.2%	Eye symptoms <sup>£</sup>	40.1%	28.5%
Practical problems	36.1%	18.2%	Practical problems <sup>£</sup>	43.3%	32.3%
Other symptoms	28.5%	19.4%	Other symptoms <sup>£</sup>		
			<i>Sleep</i>	39%	28%
			<i>Non nose or eye</i>	34.3%	24.2%
			<i>Emotional</i>	40%	29.7%
Activity limitations	33.5%	22.5%	Activity limitations <sup>£</sup>	38.3%	31.9%
Overall score	33.7%	19.2%	Overall score <sup>£</sup>	38.5%	27.5%

**Notes:** \*Baseline scores not provided by authors; <sup>€</sup>Data provided as mean (SD); <sup>£</sup>Data extrapolated from figure.

**Abbreviations:** PRQLQ, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.

with best benefit/risk ratio by assessing change in T4SS and global incidence of AEs. Patients were randomized to receive LCZ 2.5 mg (n = 117), LCZ 5 mg (n = 116), LCZ 10 mg (n = 118) or PLA (n = 119) every evening and were exposed to outside air on daily basis. Patients used a diary to track AEs and symptom severity for T4SS and nasal congestion before taking study medication each evening. At baseline, mean (SD) T4SS scores were 7.83 (2.14), 7.45 (2.07), 7.15 (2.08), and 7.94(2.06), respectively. After treatment, all three doses caused significant reduction in scores [4.37 (2.38), 4.00 (2.14), 3.37 (2.16), and 5.33 (2.46),  $P = 0.0001$  for global treatment effect, respectively] with 10 mg group experiencing most improvement. Individual symptom scores were significantly improved by those in LCZ 5 mg and 10 mg groups only ( $P < 0.002$  vs. PLA). Nasal congestion scores were not improved by LCZ at any dose. Patients in LCZ group also reported improvement in T4SS during dry weather conditions (rainy days excluded,  $P$ -values not provided). Discontinuation rates were 9%, 12%, 9%, and 24%, respectively. Lack of efficacy was the most common reason for discontinuation in PLA group vs. LCZ group (19% vs. 6.6%). AEs occurred in 29.9%, 31.9%, 44.9%, and 32.7% of patients, respectively. Common AEs were somnolence (2.6%, 1.7%, 10.2%, and 0%), fatigue (0.9%, 5.2%, 5.9%, and 1.7%), headache (6.8%, 8.6%, 9.3%, and 16%), and dry mouth (3.4%, 3.5%, 4.2%, and 2.5%), respectively. The study authors concluded LCZ 5 mg/day would reduce T4SS with less AEs than the 10 mg dose.

Ciprandi et al<sup>33</sup> conducted a 2-week, randomized, double-blind, placebo-controlled, parallel-group pilot study in Italy during pollen season in 30 patients (90% males; age range 18–34 years). The objective was to determine effect of LCZ 5 mg/day, DSL 5 mg/day or PLA on TSS, nasal airflow measured by rhinomanometry, nasal cytology (eosinophils and neutrophils), and cytokine levels (IL-4 and IL-8). Nasal lavage with saline solution was allowed for rescue. Patients randomized to LCZ reported statistically significant reduction in all outcomes vs. baseline ( $P \leq 0.041$ ); significant reduction in TSS, nasal cytology, and cytokines vs. PLA ( $P \leq 0.009$ ); and significant reduction in TSS and eosinophils vs. DSL ( $P \leq 0.008$ ). Patients in DSL group reported statistically significant reduction in TSS and IL-4 vs. baseline ( $P \leq 0.05$ ); and significant reduction in TSS, nasal cytology, and cytokines vs. PLA ( $P \leq 0.03$ ). Treatment with DSL or PLA did not affect nasal airflow from baseline. Both LCZ and DSL caused similar reduction in neutrophils and cytokine concentrations.

Mansfield et al<sup>42</sup> conducted a 2-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group study in 596 patients (24% males; age range 18–65 years) in 39 sites across United States. The objective was to evaluate effect of LCZ 5 mg/day on T5SS, RQLQ, WPAI-AS questionnaire, and ESS. Study eligibility included documented history of SAR, requiring medication, in previous 2 years; additionally those with asthma could only be using short-acting  $B_2$ -agonists as needed. No rescue medications



were allowed. Nonsignificant reduction in T5SS, RQLQ and ESS was seen in LCZ group vs. PLA. Mean (SD) baseline and adjusted mean (SE) at endpoint T5SS for LCZ vs. PLA groups were 10.74 (2.39) vs. 10.83 (2.28) and 8.9 (0.19) vs. 9.04 (0.19), respectively; adjusted mean difference between groups was  $-0.14$  [95% CI  $-0.59, 0.31$ ],  $P = 0.546$ . The mean (SD) baseline and adjusted mean (SE) at endpoint RQLQ score for LCZ vs. PLA groups were 3.57 (1.06) vs. 3.66 (1.08) and 2.45 (1.39) vs. 2.58 (1.42), respectively; adjusted mean difference between groups was  $-0.08$  [95% CI  $-0.27, 0.12$ ],  $P = 0.442$ . Mean (SD) baseline and adjusted mean (SE) at endpoint ESS for LCZ vs. PLA groups were 11.9 (4.9) vs. 12.1 (5.2) and 9.9 (5.3) vs. 10.3 (5.1), respectively; adjusted mean difference between groups was  $-0.2$  [95% CI  $-0.81, 0.42$ ],  $P = 0.532$ . Table 3 describes effect of LCZ vs. PLA on work productivity. Patients randomized to LCZ experienced reduction in percentage of work time missed, impairment while working, overall work impairment, and activity impairment due to allergy ( $P \leq 0.027$  vs. PLA). TEAEs occurred in 23.9% vs. 24.4% in LCZ vs. PLA groups. Three most frequently occurring TEAEs were headache (3.3% vs. 6.8%), somnolence (4% vs. 2.7%) and fatigue (3% vs. 1.7%), respectively. Nine patients in LCZ group vs. seven in PLA group discontinued study participation due to the following reasons: TEAEs (2 vs. 4), lack of efficacy (1 vs. 1), lost to follow-up (2 vs. 0), and other (4 vs. 2).

Segall et al<sup>43</sup> conducted a 2-week, randomized, multicenter, double-blind, placebo-controlled, parallel-group study in 580 patients (40% males; age range 27–50 years) in 39 sites across United States. The objective was to evaluate effect of LCZ 5 mg/daily on 24-hour reflective T5SS. Additional outcome measures were TNSS, TOSS (Total Ocular Symptom Score of ocular itching/burning, ocular tearing/watering, and ocular redness), global evaluation rating by patients and physicians, RQLQ, WPAI-AS questionnaire, and ESS.

Mean baseline and endpoint T5SS for LCZ vs. PLA groups were 10.55 vs. 10.44 and 7.83 vs. 8.72, respectively; adjusted mean difference vs. PLA was  $-0.89$ ,  $P < 0.001$ . Scores for sneezing, itchy eyes/nose, and rhinorrhea but not nasal congestion significantly improved with LCZ vs. PLA ( $P \leq 0.003$ ). Furthermore, significant reduction in TNSS ( $-0.74$ ,  $P < 0.001$ ) and TOSS ( $-0.54$ ,  $P < 0.001$ ) was seen for those receiving LCZ vs. PLA, with higher percentage of

patients randomized to LCZ reporting improvement in symptoms (66.2% vs. 52.9%,  $P < 0.001$ ). RQLQ scores showed those in LCZ group had significant improvement in QOL, work productivity/activity, and daytime somnolence ( $P < 0.05$ ) (Tables 2–3). TEAEs occurred in 14.4% vs. 18.4% of patients in LCZ vs. PLA groups and common AEs were headache (13 vs. 12), fatigue (5 vs. 0), dry throat (4 vs. 0), pharyngolaryngeal pain (3 vs. 2), pain (3 vs. 1), cough (2 vs. 3), and somnolence (2 vs. 3). Reasons for study discontinuation included: AEs (1 in LCZ, 2 in PLA); lack of efficacy (2 in LCZ, 1 in PLA); loss of efficacy (1 in PLA); lost to follow up (1 in PLA) and other reasons (4 in LCZ, 2 in PLA).

Barnes et al<sup>44</sup> conducted a 2-week, randomized, double-blind, placebo-controlled, crossover, non-superiority study in 27 patients (40% males; age range 16–75 years) in Scotland. The objective was to compare effects of adding LCZ 5 mg/day to 200 mcg fluticasone (FLUT) nasal spray daily vs. FLUT with PLA. Primary outcomes were Juniper mini-RQLQ, domiciliary morning peak nasal inspiratory flow rate (PNIF) to establish maximal airflow rates, TNS, and nasal nitric oxide (NO) concentrations, which is marker of airway eosinophilic inflammation. Patients were eligible if they had seasonal (intermittent or persistent) AR and grass pollen skin prick-positive response. Two-week washout period was used to establish baseline symptoms prior to treatment initiation. After randomization, patients received two weeks of FLUT nasal spray with either PLA or LCZ 5 mg, and then crossed over and received other therapy for 2 weeks. Patients were given cromoglicate nasal spray and eye drops as rescue medications, but these were not permitted within 24 hours before each visit. Patients kept diaries to record nasal symptoms each morning. Statistically significant improvements from baseline in mini-RQLQ, PNIF, and TNS were seen when patients received combination FLUT + LCZ or FLUT monotherapy. No statistically significant improvements in nasal NO levels were found. Monotherapy and combination therapy significantly reduced nasal blockage, along with other nasal symptoms from baseline ( $P < 0.01$ ); however, addition of LCZ caused significant reduction only in nasal blockage compared with monotherapy ( $P < 0.005$ ).<sup>44</sup> One patient in FLUT + LCZ reported minor epistaxis and another in FLUT + PLA reported lethargy.



**Table 3.** Effect of levocetirizine on work productivity and activity impairment-allergy specific instrument.

	Mansfield et al <sup>42</sup>				Segall et al <sup>43</sup>			
	Levocetirizine 5 mg		Placebo		Levocetirizine 5 mg		Placebo	
	Baseline Mean (SD)	Endpoint Mean (SD)	Baseline Mean (SD)	Endpoint Mean (SD)	Baseline Mean (SD)	Change from baseline <sup>f</sup>	Baseline Mean (SD)	Change from baseline <sup>f</sup>
Work time missed due to allergy, %	4.5 (12.9) (n = 235)	1.2 (4.9) <sup>y</sup>	3.5 (9.8) (n = 233)	2.3 (8.8)	3.8 (11.2) (n = 214)	2.6*	3.3 (9.42) (n = 225)	1.1
Impairment while working due to allergy, %	51.9 (24.2) (n = 227)	37.8 (21.4) <sup>*</sup>	49 (24.2) (n = 234)	40.9 (24.1)	51.6 (24.1) (n = 216)	13.4*	49.3 (24.0) (n = 227)	8.6
Overall work impairment due to allergy, %	52.9 (24.9) (n = 225)	38.2 (21.8) <sup>z</sup>	50.0 (24.6) (n = 231)	40.9 (24.1)	52.5 (24.6) (n = 214)	14*	50.1 (24.3) (n = 223)	9.4
Class time missed due to allergy, %	7.2 (17.5) (n = 29)	1.9 (5.9)	5.6 (11.0) (n = 32)	6.0 (11.7)	5.8 (13.3) (n = 22)	4.3	5.98 (11.2) (n = 30)	-0.3
Impairment in the classroom due to allergy, %	51.4 (23.6) (n = 29)	40.8 (20.4)	53.8 (29.2) (n = 32)	49.0 (23.4)	50.5 (22.9) (n = 22)	9.4	56.0 (28.6) (n = 30)	4.6
Overall classroom impairment due to allergy, %	53.7 (25.1) (n = 29)	42.0 (20.5)	55.1 (29.7) (n = 32)	51.5 (24.2)	52.7 (24.1) (n = 22)	10.3	57.4 (29.1) (n = 30)	3.7
Activity impairment due to allergy, %	57.5 (23.7) (n = 282)	39.6 (22.1) <sup>z</sup>	56.5 (22.7) (n = 288)	44.8 (24.9)	57.9 (23.8) (n = 273)	18**	56.5 (22.6) (n = 280)	12

**Notes:** <sup>a</sup>Data extrapolated from figure; <sup>y</sup>Difference vs placebo at endpoint = -1.36 [95% CI -2.56 to -0.16],  $P = 0.027$ ; <sup>z</sup>Difference vs placebo at endpoint = -4.6 [95% CI -8.34 to -0.86],  $P = 0.016$ ; <sup>\*</sup>Difference vs. placebo at endpoint = -4.44 [95% CI -8.25 to -0.63],  $P = 0.023$ ; <sup>†</sup>Difference vs placebo at endpoint = -5.91 [95% CI -9.34 to -2.47],  $P < 0.001$ ; <sup>\*\*</sup> $P < 0.001$  vs placebo.

Study authors concluded addition of LCZ to FLUT nasal spray did not further improve RQLQ, TNS or PNIF; however, patients with persistent nasal blockage symptoms may benefit from addition of LCZ to FLUT monotherapy.

Jorissen et al<sup>45</sup> conducted an open-label uncontrolled and non-randomized multi-center study in Belgium of 1290 patients (18–65 years of age) taking LCZ 5 mg/daily for 4 weeks to assess effectiveness and safety in relieving symptoms. Primary endpoints were T4SS, change in Clinical Global Impression (CGI-c) rated by general practitioner (GP), and patient-reported satisfaction with and preference for LCZ. Investigators did not evaluate nasal obstruction due to study's short duration. Sixty-one percent of patients reported not using any medications before study, 36.4% received antihistamines and 2.3% used other SAR medications (nasal steroid spray, nasal decongestant spray). Patients were placed into one of four subgroups: patients previously treated with any antihistamines and patients previously treated with particular antihistamine [CET, loratadine (LOR) or DSL].

After 4 weeks, statistically significant reduction in mean (SD) T4SS from baseline [8.24 (1.71) to 2.66 (1.93),  $P < 0.001$ ] was observed for all patients. Additionally, significant improvement was seen in patients who did not receive antihistamines in the past ( $n = 820$ ) or who were previously on CET ( $n = 162$ ), LOR ( $n = 126$ ), or DSL ( $n = 57$ ). Physicians reported 88% of patients previously treated with other antihistamines showed significant improvement by CGI-c ( $P < 0.01$ ), while >90% of patients reported satisfaction with LCZ therapy ( $P < 0.01$ ). Preference for LCZ over CET, LOR and DSL in the future was reported by 77% of patients. Forty percent and 28% of patients previously on CET reported somnolence and fatigue, respectively, at baseline and this number was reduced to 10% for both AEs, after LCZ therapy.

Maiti et al<sup>46</sup> conducted a 2-week, randomized, single-center, open, parallel-group study in 60 patients (55% males; age range 12–50 years) randomized to rupatadine 10 mg/day (RUP) vs. LCZ 10 mg/day in India. Primary efficacy endpoints were change in TNSS, RQLQ (patients  $\geq 18$  years of age) or PRQLQ (patients 12–17 years of age), and anti-inflammatory markers. RUP is second-generation antihistamine with anti-platelet activating factor activity. Mean



(SD) baseline TNSS and RQLQ scores were 15 (3.4) vs. 13.8 (2.8) and 3.65 (1.25) vs. 3.12 (0.89), respectively. Both agents caused significant improvement in TNSS and RQLQ from baseline ( $P \leq 0.003$ ), but RUP was more effective than LCZ for TNSS [95% CI  $-2.24$  to  $-0.81$ ,  $P < 0.001$ , unpaired t-test] and RQLQ scores [95% CI  $-0.64$  to  $-0.06$ ,  $P = 0.02$ ]. A 25% reduction in TNSS and RQLQ was seen in 21 and 17 patients on RUP vs. 12 and 8 patients on LCZ ( $P \leq 0.03$  for both comparisons), respectively. RUP was associated with statistically significant reduction in total leukocyte count, differential neutrophil count, differential eosinophil count, absolute eosinophil count, and IgE levels ( $P \leq 0.007$  vs. baseline). LCZ was associated with statistically significant reduction only in differential eosinophil count, absolute eosinophil count, and IgE levels ( $P \leq 0.001$  vs. baseline). RUP was more effective than LCZ at reducing differential eosinophil count, absolute eosinophil count, and IgE levels ( $P \leq 0.004$ ). Incidence of AEs was 11.5% vs. 23.3% in RUP vs. LCZ groups, with most frequently reported AEs in both groups being fatigue, headache and dry mouth. Three patients from LCZ group reported drowsiness. One patient from each group withdrew due to an AE (moderate headache in a patient on RUP and moderate dryness of mouth in a patient on LCZ).

## Tolerability

Hampel et al<sup>34</sup> reviewed safety and tolerability of LCZ oral liquid drops in infants ( $n = 69$ , aged 6–11 months) and children ( $n = 173$ , aged 1–5 years) with AR or chronic idiopathic urticaria in two randomized, double-blind, placebo-controlled, parallel-group studies. TEAEs, vital signs, ECG assessments, and laboratory tests were reviewed. Infants received LCZ 1.25 mg/daily ( $n = 45$ ) or PLA ( $n = 24$ ) and children received LCZ 1.25 mg twice daily ( $n = 114$ ) or PLA ( $n = 59$ ) for 2 weeks. Eight patients did not complete studies (LCZ groups: 3 infants were withdrawn due to TEAEs, 2 children for lack/loss of efficacy, withdrawal of consent by 1 child for reasons not related to TEAEs; PLA groups: withdrawal of consent for reasons not related to TEAEs by 1 infant and 1 child). In infant study, 29 (64.4%) patients in LCZ vs. 17 (70.8%) patients in PLA group reported 54 vs. 34 TEAEs (mostly of mild to moderate severity), respectively. Frequently reported TEAEs

were diarrhea (6 vs. 1), constipation (3 vs. 1), skin rash (6 vs. 7), respiratory (4 vs. 4) and somnolence (2 vs. 1), respectively. In children study, 40 (35.1%) vs. 21 (35.6%) patients experienced 60 vs. 43 TEAEs, respectively. Frequently reported TEAEs were pyrexia (5 vs. 1), otitis media (3 vs. 0), diarrhea (4 vs. 2), respiratory disorders (9 vs. 6), and skin disorders (5 vs. 1), respectively. No clinically relevant changes from baseline were found with regard to vital signs or laboratory parameters in either study. One child in each treatment group experienced elevated AST/ALT levels and authors did not consider elevations significant in child that received PLA. However, a child in LCZ group who experienced AST/ALT elevations was also receiving cefixime which is known to cause this elevation. ALT values normalized 24 days later. Eleven patients in LCZ groups (7 infants, 4 children) and 3 in PLA groups (3 infants) experienced new ECG abnormalities. In infant group, all abnormalities resolved during last treatment visit, except for left axis deviation. In children study, 1 child had sinus bradycardia, 2 had sinus tachycardia, and 1 had right bundle branch block.

Simons et al<sup>51</sup> conducted an 18-month, prospective, randomized, double-blind, placebo-controlled study regarding safety of LCZ 0.125 mg/kg twice daily in 510 children (12–24 months old) with atopic dermatitis. Researchers assessed AEs, discontinuation due to AEs, and developmental milestones (physical and psychological). AEs occurred in 96.9% vs. 95.7% of patients in LCZ vs. PLA groups, but investigators reported AEs due to treatment were only 5.1% vs. 6.3%, respectively. Common AEs included upper respiratory tract infections (51% vs. 50%), nasopharyngitis (30% vs. 28%), pyrexia (35% vs. 28%), gastroenteritis (24% vs. 24%), viral infections (10% vs. 10%), influenza (12% vs. 5%), AR (10% vs. 6%), and atopic dermatitis (6% vs. 7%).

Serious AE occurred in 12.2% vs. 14.5% of patients, respectively and included wheezing (4.7% vs. 7.5%) and febrile convulsions (occurred in 5 infants who received LCZ vs. 1 in PLA group).<sup>51</sup>

Konstantinou et al<sup>52</sup> submitted a case report of 34-year-old male who presented to emergency department due to rapid-onset intense pain in left eye, photophobia and blurred vision. Patient denied any eye injury, similar symptoms in past or taking any other medications other than LCZ 5 mg night



prior to onset of eye symptoms (patient received LCZ for several days prior to onset of ocular symptoms). Lab values (complete blood count and erythrocyte sedimentation rate) were within normal range, but upon ophthalmic exam he was found to have bulbar conjunctivitis and impaired visual acuity in left eye. Iridocyclitis was concluded once patient had slit lamp examination and fundoscopy. Topical dexamethasone (4 times/day) was used for treatment and patient decided to discontinue LCZ. Symptoms disappeared four days later and a full ophthalmic recovery at follow-up appointment (7 days after incident) was determined. Patient was re-challenged 10 days later with LCZ taken at 10 PM and same symptoms occurred following morning with resolution 4 days later.

Hulhoven et al<sup>53</sup> conducted a single-dose, placebo and positive-controlled, four-way crossover, randomized trial in 52 patients (age range 18.4–46 years) in Belgium. The objective was to conduct thorough QT study of LCZ based on International Conference of Harmonization (ICH) E14 guidance. Patients were double-blinded to LCZ (5 mg and 30 mg) and PLA; however moxifloxacin (400 mg) was open-label. Moxifloxacin served as the positive control due to its demonstrated prolonged cardiac repolarization. Researchers concluded no relationship between measured change QT study-specific correction and LCZ plasma concentration, therefore no suggestion of dose- or concentration-response relationship. Absence of effect was observed on cardiac repolarization at therapeutic and supra-therapeutic doses of LCZ.

Layton et al<sup>54</sup> conducted a retrospective analysis of selected prescription-event monitoring (PEM) studies in patients (median age 37 years, ~60% women) prescribed LCZ 5 mg/daily ( $n = 12,367$ ) or DSL 5 mg/daily ( $n = 11,828$ ) in two large cohorts followed by primary physicians in United Kingdom. The objective was to compare frequency of reported drowsiness and sedation for LCZ and DSL. Within first 30 days after starting treatment, occurrence of sedation and drowsiness for LCZ vs. DSL (46 [0.37%] vs. 9 [0.08%] cases, respectively) was significantly different ( $P < 0.0001$ ).

Verster et al<sup>55,56</sup> conducted a double-blind, placebo-controlled, randomized, crossover clinical trial in 48 patients (50% males; mean  $\pm$  SEM age was

$23.3 \pm 2.2$  years) randomized to receive LCZ 5 mg, diphenhydramine (DPH) 50 mg or PLA daily. Objectives were to investigate effects of LCZ, DPH, and PLA on driving ability during normal traffic and memory functioning and psychomotor performance on two occasions (day 1 vs. day 4). On both days, amount of car weaving, as measured by standard deviation of lateral position was similar between LCZ and PLA, but increased when patients received DPH ( $P < 0.0003$  DPH vs. PLA). Patients' perceived quality of driving showed no changes with LCZ or PLA, but when patients received DPH, there was reduction in driving quality, increased mental effort during driving, and reduced alertness on day 1 ( $P < 0.0001$  DPH vs. PLA) and reduced alertness on day 4 ( $P < 0.005$  DPH vs. PLA).

Results from ARCI-49<sup>57</sup> (see Table 1) for LCZ vs. PLA were reported as not significantly different; however, DPH scores significantly increased for sedation (days 1 and 4) and decreased in euphoria/intellectual efficacy and energy (DPH vs. PLA,  $P < 0.025$ ). Psychometric test battery results (word-learning, tracking, Sternberg Memory Scanning and divided attention tests) were used to test memory and psychomotor functioning. On day 1, divided attention and track tests were significantly different between DPH vs. PLA ( $P < 0.025$ ). However on day 4, no significant difference was found between the three groups on word-learning, divided attention, tracking or Sternberg Memory Scanning Test. Researchers concluded DPH significantly impaired psychomotor functioning and caused sedation, whereas LCZ did not impair memory or psychomotor functioning.

## Drug Interactions

Formal in vivo drug interaction studies have not been performed with LCZ, only with racemic cetirizine.<sup>7</sup> Based on in vitro information on metabolite interaction, LCZ unlikely produced or was affected by metabolic interactions.<sup>7</sup> Metabolism is a minor elimination pathway for LCZ; therefore LCZ is less likely to interact through inhibition.<sup>7,58</sup> Even at concentrations above  $C_{max}$  level, LCZ does not inhibit CYP isoenzymes 1A2, 2C9, 2C19, 2A1, 2D6, 2E1, and 3A4, and does not induce UGT1A or CYP isoenzymes 1A2, 2C9 and 3A4.<sup>7,13</sup> In vitro inhibitory potency of therapeutic doses of LCZ were not likely to inter-



fare with metabolic clearance of other medications administered in clinical concentrations.<sup>7</sup>

## Dosing and Administration

LCZ was approved in United States in May 2007 and is available as immediate-release formulations: scored 5 mg tablets and oral solution 2.5 mg/5 mL.<sup>7</sup> Evening administration is suggested by manufacturer without regard to meals.<sup>7</sup> Dosing for children 6 months to 5 years is 1.25 mg/daily in evening and 2.5 mg/daily in evening for children 6 to 11 years old.<sup>7</sup> In patients  $\geq 12$  years, suggested dose is 5 mg/daily in the evening.<sup>7</sup> Dose adjustment for renal impairment in adults and  $\geq 12$  years is based on the patient's creatinine clearance ( $CL_{CR}$ ).<sup>7</sup> Dosing for renal impairment is as follows: 2.5 mg daily for  $CL_{CR}$  of 50–80 mL/min, 2.5 mg every other day for  $CL_{CR}$  of 30–50 mL/min, and 2.5 mg twice weekly (dosed once every 3–4 days) for  $CL_{CR}$  of 10–30 mL/min.<sup>7</sup> Dose adjustment is not necessary if patients only have hepatic impairment.<sup>7</sup> However, dosage adjustment is recommended in patients with both hepatic and renal impairment.<sup>7</sup> Use of LCZ is contraindicated in following patients: known hypersensitivity to LCZ or ingredients of LCZ or CET; end-stage renal disease ( $CL_{CR} < 10$  mL/min) and undergoing hemodialysis; children 6 months to 11 years with impaired renal function.<sup>7</sup>

## Pharmacoeconomic Considerations

Average wholesale price for 148-mL bottle of brand LCZ 2.5 mg/5 mL solution is \$102.55, and two-week supply of 5 mg tablets is \$47.86.<sup>59</sup> Of note, Synthon Pharmaceuticals, Inc., recently received FDA approval for generic version of Xyzal® and AWP for month's supply is \$92.30 with 2-week supply costing \$43.07.<sup>60</sup> Therefore, average daily cost/dose is \$6.93/10 mL, \$3.42/brand 5 mg tablet, and \$3.08/5 mg generic tablet, respectively.

Two articles addressing economic impact of LCZ use in AR were identified.<sup>61,62</sup> Goodman et al conducted a cost-effectiveness analysis of LCZ vs. DSL, generic and brand fexofenadine (FEX), and MLK. Twenty-five randomized, placebo-controlled studies in patients  $> 12$  years of age with SAR or PAR (but not asthma) of  $\geq 7$  days were used to populate decision analytic model. Effectiveness outcome was composite NSS (average effect size of each active agent vs.

PLA) for rhinorrhea, sneezing, and nasal congestion. Because this analysis was from managed care organization's (MCO) perspective, only direct costs were included and lost productivity and over-the-counter (OTC) medication costs were excluded. Direct costs consisted of 90 day cost of medication therapy and physician office visits, gathered using PharMetrics dataset and extrapolated over the course of one year and calculated in 2007 US dollars. Incremental cost-effectiveness ratios (ICER) or ratio of difference in cost to difference in probability of significant improvement in symptoms, were calculated to report comparisons in model. LCZ was less costly and more effective than other medications. Monte Carlo simulation supported base case results. ICERs for branded and generic FEX vs. LCZ were not considered to be significant due to overlap of CI with 0.0 (DSL  $-2107$  [95% CI  $-4596, -82$ ]; generic FEX  $-205$  [95% CI  $-3134$  to  $2389$ ]; brand FEX  $-1689$  [95% CI  $-5393$  to  $797$ ]; MLK  $-4064$  [95% CI  $-4064$  to  $858$ ]).<sup>61</sup>

Saverno et al conducted a cost-effectiveness analysis, using model similar in construction to Goodman et al, of LCZ vs. DSL, generic and brand FEX, and MLK for treatment of AR. In this analysis, effectiveness was assessed as clinically relevant improvement in RQLQ. Analysis also included direct medical costs only (drug cost and physician office visits), and excluded lost productivity and cost of OTC medications. Eleven studies were used to populate decision analytic model. Mean QOL effect sizes based on RQLQ showed similar outcomes, but LCZ showed most improvement in QOL ( $-0.418$  [95% CI  $-0.573, -0.262$ ]), followed by DSL ( $-0.360$  [95% CI  $-0.539, -0.180$ ]), MLK ( $-0.213$  [95% CI  $-0.267, -0.159$ ]) and FEX ( $-0.201$  [95% CI  $-0.301, -0.101$ ]). Based on calculated ICER in comparison to LCZ, generic FEX was found to cost less and be less effective than LCZ (generic FEX  $361$  [95% CI  $-1166$  to  $3574$ ]). Remaining second-generation anti-histamines and MLK were all more expensive and less effective than LCZ (DSL  $-2189$  (95% CI  $-10,138$  to  $17,275$ ); brand FEX  $-198$  [95% CI  $-3241$  to  $1186$ ]; MLK  $-1317$  [95% CI  $-7471, -212$ ]).<sup>62</sup>

## Discussion

LCZ, the active R-enantiomer of CET, is highly-selective, high-affinity, second-generation  $H_1$  receptor



antagonist indicated for treatment of SAR, PAR and skin manifestations of chronic idiopathic urticaria.<sup>7,63</sup> It is rapidly and extensively absorbed, has a low  $V_D$ , and is eliminated primarily through renal excretion.<sup>12,14</sup> Evidence of anti-inflammatory effect is conflicting due to variety of measured immunologic parameters, inconsistent results and disconnect from efficacy measures.<sup>31–33</sup> Under controlled conditions of an EEU or EEC, anti-histaminic effects of LCZ were seen in wheal-and-flare responses vs. PLA, DSL, and MLK<sup>18–20</sup> although these wheal-and-flare tests may not be the best way to prove clinical efficacy of medications used to treat AR.<sup>64</sup>

Eight studies, examining 3230 patients, were included in this review of efficacy and QOL of LCZ in patients with SAR. Four studies compared LCZ with PLA,<sup>40–43</sup> one study compared LCZ with RUP,<sup>46</sup> one study compared LCZ and DSL with PLA,<sup>33</sup> one study assessed LCZ in patients naïve to or were on previous antihistamine therapy,<sup>45</sup> and another study compared FLUT monotherapy with FLUT + LCZ.<sup>44</sup> LCZ was superior to PLA in three studies<sup>40,41,43</sup> and equal in efficacy in one study.<sup>42</sup> RUP was superior to LCZ<sup>46</sup> and addition of LCZ to FLUT therapy was equal to FLUT monotherapy.<sup>44</sup> When all patients (antihistamine naïve or previously-exposed) received LCZ, there was a significant reduction in symptoms with greater satisfaction compared with previous therapy.<sup>45</sup>

It is difficult to draw conclusions on the effect of LCZ due to the wide variety of efficacy outcomes in clinical trials varying from T5SS, T4SS, TOSS, TNS/TSS, TNSS, nasal NO, inflammatory cells, cytokine, RQLQ, ESS, WPAI-AS, nasal air-flow, PNIF and global evaluation. Since efficacy endpoints lack standardization, a more effective manner to monitor efficacy may be to review individual symptoms.

Five<sup>33,40,41,43,45</sup> studies concluded that LCZ significantly improved TNS, TSS, TNSS, T4SS and/or T5SS. In the multiple-dose study, investigators found individual symptom scores significantly improved in those taking LCZ 5 mg or 10 mg vs. PLA.<sup>41</sup> In two studies which reviewed effect of LCZ on T5SS, one found T5SS (except nasal congestion) was significantly improved with LCZ along with TNSS and TOSS vs. PLA,<sup>43</sup> whereas the other found non-significant reduction in T5SS by LCZ vs. PLA.<sup>42</sup> In

the 6-week pediatric study reviewed,<sup>40</sup> LCZ relieved nasal congestion significantly better than PLA only at week 3, but had significant improvement in all T4SS (except ocular pruritus) over 6 weeks.

Nasal congestion was reported as not improved by LCZ in two studies<sup>41,43</sup> and improved by LCZ in another two studies.<sup>33,40</sup> Barnes et al<sup>44</sup> reported significant reduction in nasal blockage with addition of LCZ to FLUT vs. FLUT monotherapy ( $P < 0.005$ ); therefore addition of LCZ to FLUT monotherapy may benefit patients with persistent nasal blockage symptoms while also using FLUT therapy.<sup>44</sup> Ciprandi et al<sup>33</sup> reported decrease in nasal obstruction scores for LCZ and DSL, but not PLA. These results regarding nasal congestion are inconsistent and more research is needed.

Two studies<sup>33,46</sup> assessed eosinophils and neutrophils. Study comparing LCZ and DSL to PLA found significant reduction in nasal cytology and cytokines vs. PLA ( $P \leq 0.007$ ) and significant reduction and eosinophils vs. DSL ( $P \leq 0.008$ ).<sup>33</sup> LCZ and DSL groups both caused a similar reduction in neutrophils and cytokine (IL-4 and IL-8) concentrations.<sup>33</sup> However, when LCZ was compared to RUP for anti-inflammatory activity, RUP was more effective than LCZ at reducing eosinophil counts (differential and absolute), IgE levels, total leukocyte count and differential neutrophil count ( $P \leq 0.02$ ).<sup>46</sup>

Four studies reviewed RQLQ,<sup>40,42,43,46</sup> and two studies<sup>42,43</sup> assessed WPAI-AS and ESS. Two placebo-controlled studies and study with RUP as comparator did not find LCZ to significantly improve RQLQ;<sup>40,42,46</sup> only one study found LCZ to significantly improve this outcome.<sup>43</sup> Both Segal et al<sup>43</sup> and Mansfield et al<sup>42</sup> found that LCZ significantly improved work-related component scores but not classroom-related scores; however, only one study reported less complaints of daytime sleepiness with LCZ compared with PLA.<sup>43</sup>

In 7 studies<sup>40–46</sup> (2 to 6 weeks in duration), AEs were reported in 369 of 2374 patients (15.5%) who received LCZ. Frequent AEs for the LCZ group included somnolence (26.7%), fatigue (24.6%), headache (20%), dry mouth/throat (14.7%) and epistaxis (1.6%). Patients who were previously treated with CET reported having fatigue and somnolence at rates of 40% and 28%, respectively and experienced a 10% decrease in AEs with LCZ.<sup>45</sup> Five studies<sup>40–44</sup> reported a total of 64 patients who withdrew or



discontinued LCZ therapy. Of 65 patients who discontinued/withdrew, the most common reasons for discontinuation/withdrawal were: lack of efficacy 40% (n = 26), AE 13.8% (n = 9), lost to follow-up 3% (n = 2), other reasons and not reported 43.1% (n = 28).<sup>40-44</sup> Simon et al<sup>51</sup> reported an increased number of febrile seizures in infants taking LCZ and we did not find any reports of fetal malformations with LCZ use during pregnancy. A study to determine effect of LCZ on driving found that LCZ was not associated with increased car weaving, memory deficits, and mood changes after 1st and 4th dose compared with DPH.<sup>55,56</sup> Additionally, LCZ did not cause QT prolongation or effect cardiac repolarization at therapeutic or supra-therapeutic doses.<sup>53</sup>

Two studies<sup>61,62</sup> examined the cost-effectiveness of LCZ in AR for use in adults, and found this agent an economically-viable option compared to other second-generation antihistamines and MLK. Efficacy measures included a composite score of nasal symptoms (rhinorrhea, sneezing, and nasal obstruction) and RQLQ. The two studies were similarly structured, but neither study included pediatric patients or indirect medical costs as a part of their model. Construction of cost-effectiveness models from MCO perspective used in the studies limits applicability to clinicians. This more narrow view neglects common indirect costs, such as absenteeism and presenteeism (defined as a decrease in productivity at work or school), which are a significant part of the economic burden in AR.<sup>65,66</sup> Furthermore, patients often choose to self-treat by using OTC medications, either alone or in combination with prescription medications, but these costs are also absent in MCO perspective model.<sup>1</sup> Ideally, cost-effectiveness decision models are replicable and transparent.<sup>67</sup> For the two articles studied, assessing event pathway in decision model is difficult as a diagram was not provided. Additionally, methods for obtaining effectiveness outcome calculation, or SMD, are unclear based on description provided by authors, making determination of appropriateness of calculation and interpretation of results difficult. Lastly, because children <12 years of age were excluded from both studies it is difficult to establish if LCZ is a cost-effective treatment option in this population, which highlights the necessity of a pharmacoeconomics component to long-term studies in children.

In a 6-month, multicenter, multinational study assessing use of LCZ 5 mg/day vs. PLA in adult patients with PAR, including a pharmacoeconomic analysis, was conducted by the Xyzal in Persistent Rhinitis Trail (XPRT) panel.<sup>68</sup> At four weeks, a significant improvement in T5SS was seen in patients given LCZ vs. PLA (adjusted mean 1.14 [95% CI 0.29, 0.67];  $P < 0.001$ ). Compared with PLA, patients who took LCZ experienced less absenteeism (0.18 days vs. 0.45 days) and presenteeism (0.70 days vs. 1.11 days). After a French societal cost model was applied to outcomes, investigators concluded per patient per month combined direct and indirect costs of LCZ were 33% lower than PLA (€108.18 vs. €160.27;  $P = 0.008$ ).<sup>68</sup> This large, multicenter trial supports cost-effective use of LCZ for treatment of PAR. In the future, long-term data on the economic benefit of LCZ (including the generic) use in SAR would provide information to clinicians and MCO as a complement to efficacy data.

## Conclusions

LCZ was efficacious, well-tolerated, and improved quality of life in adults and children. Nasal symptoms (rhinorrhea, nasal pruritus and sneezing) were improved with use of LCZ; however LCZ's effect on nasal congestion/obstruction was inconclusive. Adverse events included somnolence and fatigue. It is difficult to conclude LCZ's cost-effectiveness and anti-inflammatory properties without additional studies. Finally, studies about LCZ's safety in infants and in comparison with other anti-histamines are needed to further clarify its' efficacy and tolerability profile.

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## References

1. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA<sup>2</sup>LEN. *Allergy*. 2008;63:8–160.
2. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *Am J Respir Crit Care Med*. 2000 Oct 1;162(4):1391–6.
3. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy*. 2005;60(3):350–3.
4. Nathan RA, Meltzer EO, Derebery J, et al. The prevalence of nasal symptoms attributed to allergies in the United States: findings from the burden of rhinitis in an America survey. *Allergy and Asthma Proceedings: The Official Journal of Regional and State Allergy Societies*. 2008;29(6):600–8.
5. Ghouri N, Hippisley-Cox J, Newton J, Sheikh A. Trends in the epidemiology and prescribing of medication for allergic rhinitis in England. *J R Soc Med*. 2008 Sep 1;101(9):466–72.
6. Van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement\* on the treatment of allergic rhinitis. *Allergy*. 2000;55(2):116–34.
7. Xyzal [package insert]. Smyrna, GA: UCB Pharma, Inc.; August 2009.
8. Leurs R, Church MK, Tagliabue M. H<sub>1</sub>-antihistamines: inverse agonism, anti-inflammatory actions and cardiac effects. *Clinical and Experimental Allergy: Journal of The British Society for Allergy and Clinical Immunology*. 2002;32(4):489–98.
9. Broide DH. The pathophysiology of allergic rhinoconjunctivitis. *Allergy and Asthma Proceedings*. 2007;28:398–403.
10. Pearlman DS. Pathophysiology of the inflammatory response. *The Journal of Allergy and Clinical Immunology*. 1999;104(4):s132–7.
11. Prussin C, Metcalfe DD. 5. IgE, mast cells, basophils, and eosinophils. *Journal of Allergy and Clinical Immunology*. 2006;117(2 Suppl 2):S450–6.
12. Strolin Benedetti M, Plisnier M, Kaise J, et al. Absorption, distribution, metabolism and excretion of [<sup>14</sup>C]levocetirizine, the R enantiomer of cetirizine, in healthy volunteers. *European Journal of Clinical Pharmacology*. 2001;57(8):571–82.
13. Baltes E, Coupeux R, Giezek H, Voss G, Meyerhoff C, Benedetti MS. Absorption and disposition of levocetirizine, the enantiomer of cetirizine, administered alone or as cetirizine to healthy volunteers. *Fundamental and Clinical Pharmacology*. 2001;15(4):269–77.
14. Strolin Benedetti M, Whomsley R, Mathy FX, Jacques P, Espie P, Canning M. Stereoselective renal tubular secretion of levocetirizine and dextrocetirizine, the two enantiomers of the H<sub>1</sub>-antihistamine cetirizine. *Fundamental and Clinical Pharmacology*. 2008;22(1):19–23.
15. Tillement JP. The advantages for an H<sub>1</sub> antihistamine of a low volume of distribution. *Allergy*. 2000;55:17.
16. Bree F, Thiault L, Gautiers G, et al. Blood distribution of levocetirizine, a new non-sedating histamine H<sub>1</sub>-receptor antagonist, in humans. *Fundamental and Clinical Pharmacology*. 2002;16(6):471–8.
17. Molimard M, Diquet B, Benedetti MS. Comparison of pharmacokinetics and metabolism of desloratadine, fexofenadine, levocetirizine and mizolastine in humans. *Fundamental and Clinical Pharmacology*. 2004;18(4):399–411.
18. Day JH, Briscoe MP, Rafeiro E, Ratz JD. 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*. 2004;58(2):109–18.
19. Patel P, Patel D. Efficacy comparison of levocetirizine vs. montelukast in ragweed sensitized patients. *Annals of Allergy, Asthma and Immunology Official Publication of the American College of Allergy, Asthma, and Immunology*. 2008;101(3):287–94.
20. Passalacqua G, Guerra L, Compalati E, et al. Comparison of the effects in the nose and skin of a single dose of desloratadine and levocetirizine over 24 hours. *International Archives of Allergy and Immunology*. 2004;135(2):143–7.
21. Akdis CA, Simons FER. Histamine receptors are hot in immunopharmacology. *European Journal of Pharmacology*. 2006;533(1–3):69–76.
22. Gillard M, Christophe B, Weis B, Peck M, Massingham R, Chatelain P. H<sub>1</sub> antagonists: receptor affinity versus selectivity. *Inflammation Research*. 2003;52(Suppl 1):s49–50.
23. Gillard M, van der Perren C, Moguevsky N, Massingham R, Chatelain P. Binding characteristics of cetirizine and levocetirizine to human H<sub>1</sub> histamine receptors: contribution of Lys191 and Thr194. *Molecular Pharmacology*. Feb 1 2002;61(2):391–9.
24. Devillier P, Roche N, Faisy C. Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and levocetirizine: a comparative review. *Clinical Pharmacokinetics*. 2008;47(4):217–30.
25. Gillard M, Chatelain P. Changes in pH differently affect the binding properties of histamine H<sub>1</sub> receptor antagonists. *European Journal of Pharmacology*. 2006;530(3):205–14.
26. Menzies-Gow A, Ying S, Phipps S, Kay AB. Interactions between eotaxin, histamine and mast cells in early microvascular events associated with eosinophil recruitment to the site of allergic skin reactions in humans. *Clinical and Experimental Allergy: Journal of The British Society For Allergy and Clinical Immunology*. 2004;34(8):1276–82.
27. Petecchia L, Serpero L, Silvestri M, Sabatini F, Scarso L, Rossi GA. The histamine-induced enhanced expression of vascular cell adhesion molecule-1 by nasal polyp-derived fibroblasts is inhibited by levocetirizine. *American Journal of Rhinology*. 2006;20(5):445–9.
28. Jang YJ, Wang JH, Kim JS, Kwon HJ, Yeo N-K, Lee B-J. Levocetirizine inhibits rhinovirus-induced ICAM-1 and cytokine expression and viral replication in airway epithelial cells. *Antiviral Research*. 2009;81(3):226–33.
29. Wu P, Mitchell S, Walsh GM. A new antihistamine levocetirizine inhibits eosinophil adhesion to vascular cell adhesion molecule-1 under flow conditions. *Clinical And Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*. 2005;35(8):1073–9.
30. Giustizieri ML, Albanesi C, Fluhr J, Gisondi P, Norgauer J, Girolomoni G. H<sub>1</sub> histamine receptor mediates inflammatory responses in human keratinocytes. *The Journal of Allergy and Clinical Immunology*. 2004;114(5):1176–82.
31. Hasala H, Janka-Junttila M, Moilanen E, Kankaanranta H. Levocetirizine and cytokine production and apoptosis of human eosinophils. *Allergy and Asthma Proceedings: The Official Journal of Regional and State Allergy Societies*. 2007;28(5):582–91.
32. Mahmoud F, Arifhodzic N, Haines D, Novotney L. Levocetirizine modulates lymphocyte activation in patients with allergic rhinitis. *Journal of Pharmacological Sciences*. 2008;108(2):149–56.
33. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca MA. Levocetirizine improves nasal obstruction and modulates cytokine pattern in patients with seasonal allergic rhinitis: a pilot study. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*. 2004;34(6):958–64.
34. Hampel FC, Kittner B, van Bavel JH. Safety and tolerability of fexofenadine hydrochloride, 15 and 30 mg, twice daily in children aged 6 months to 2 years with allergic rhinitis. *Annals of Allergy, Asthma and Immunology: Official Publication of the American College of Allergy, Asthma, and Immunology*. 2007;99(6):549–54.
35. Schad CA, Skoner DP. Antihistamines in the pediatric population: achieving optimal outcomes when treating seasonal allergic rhinitis and chronic urticaria. *Allergy and Asthma Proceedings: The Official Journal of Regional and State Allergy Societies*. 2008;29(1):7–13.
36. Simons FER. Population pharmacokinetics of levocetirizine in very young children: the pediatricians' perspective. *Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology*. 2005;16(2):97–103.
37. Cranswick N, Turzikova J, Fuchs M, Hulhoven R. Levocetirizine in 1–2 year old children: pharmacokinetic and pharmacodynamic profile. *International Journal of Clinical Pharmacology and Therapeutics*. 2005;43(4):172–7.



38. Simons FER, Simons KJ. Levocetirizine: pharmacokinetics and pharmacodynamics in children age 6 to 11 years. *The Journal of Allergy and Clinical Immunology*. 2005;116(2):355–61.
39. Callaghan ML. The use of newer asthma and allergy medications during pregnancy. *Annals of Allergy, Asthma and Immunology*. 2000;84(5):475–80.
40. de Blic J, Wahn U, Billard E, Alt R, Pujazon M-C. Levocetirizine in children: evidenced efficacy and safety in a 6-week randomized seasonal allergic rhinitis trial. *Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology*. 2005;16(3):267–75.
41. Leynadier F, Mees K, Arendt C, Pinelli ME. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. *Acta Oto-Rhino-Laryngologica Belgica*. 2001;55(4):305–12.
42. Mansfield LE, Hampel F, Haeusler J-MC, Georges G. Study of levocetirizine in seasonal allergic rhinitis. *Current Medical Research and Opinion*. 2010;26(6):1269–75.
43. Segall N, Gawchik S, Georges G, Haeusler J-MC. Efficacy and safety of levocetirizine in improving symptoms and health-related quality of life in US adults with seasonal allergic rhinitis: a randomized, placebo-controlled study. *Annals of Allergy, Asthma and Immunology: Official Publication of the American College of Allergy, Asthma, and Immunology*. 2010;104(3):259–67.
44. Barnes ML, Ward JH, Fardon TC, Lipworth BJ. Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*. 2006;36(5):676–84.
45. Jorissen M, Bertrand B, Stiels B, Vandenbulcke K. Levocetirizine as treatment for symptoms of seasonal allergic rhinitis. *B-ENT*. 2006;2(2):55–62.
46. Maiti R, Rahman J, Jaida J, Allala U, Palani A. Rupatadine and levocetirizine for seasonal allergic rhinitis: a comparative study of efficacy and safety. *Archives of Otolaryngology—Head and Neck Surgery*. 2010;136(8):796–800.
47. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology*. 1991;21(1):77–83.
48. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. *The Journal of Allergy and Clinical Immunology*. 1998;101(2 Pt 1):163–70.
49. Reilly MC, Zbrozek AS, Dukas EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353–65.
50. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540–5.
51. Simons FE; Early Prevention of Asthma in Atopic Children Study Group. Safety of levocetirizine treatment in young atopic children: An 18-month study. *Pediatric Allergy and Immunology: Official Publication of the European Society of Pediatric Allergy and Immunology Official Publication of the European Society of Pediatric Allergy and Immunology*. 2007;18(6):535–42.
52. Konstantinou GN, Ligerou M, Ligeros MP. Levocetirizine-induced iridocyclitis in a patient with allergic rhinitis. *Journal of Investigational Allergology and Clinical Immunology: Official Organ of the International Association of Asthmology (INTERASMA) And Sociedad Latinoamericana De Alergia E Inmunología*. 2010;20(1):90–1.
53. Hulhoven R, Rosillon D, Letiexhe M, Meeus M-A, Daoust A, Stockis A. Levocetirizine does not prolong the QT/QTc interval in healthy subjects: results from a thorough QT study. *European Journal of Clinical Pharmacology*. 2007;63(11):1011–7.
54. Layton D, Wilton L, Boshier A, Cornelius V, Harris S, Shakir SA. Comparison of the risk of drowsiness and sedation between levocetirizine and desloratadine: a prescription-event monitoring study in England. *Drug Safety: An International Journal of Medical Toxicology and Drug Experience*. 2006;29(10):897–909.
55. Verster JC, de Weert AM, Bijtjes SIR, et al. Driving ability after acute and sub-chronic administration of levocetirizine and diphenhydramine: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology*. 2003;169(1):84–90.
56. Verster JC, Volkerts ER, van Oosterwijk AWAA, et al. Acute and sub-chronic effects of levocetirizine and diphenhydramine on memory functioning, psychomotor performance, and mood. *The Journal of Allergy and Clinical Immunology*. 2003;111(3):623–7.
57. Hill HE, Haertzen CA, Wolbach AB Jr, Miner EJ. The addiction research center inventory: standardization of scales which evaluate subjective effects of morphine, amphetamine, pentobarbital, alcohol, LSD-25, pyrahexyl and chlorpromazine. *Psychopharmacologia*. 1963;4:167–83.
58. Watelet J-B, Gillard M, Benedetti MS, Lelièvre B, Diquet B. Therapeutic management of allergic diseases. *Drug Metabolism Reviews*. 2009;41(3):301–43.
59. *Drug Topics Red Book*. Montvale, NJ: Thomson Healthcare; 2010.
60. Orange Book. <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed December 30, 2010.
61. Goodman MJ, Jhaveri M, Saverno K, Meyer K, Nightengale B. Cost-effectiveness of second-generation antihistamines and montelukast in relieving allergic rhinitis nasal symptoms. *American Health and Drug Benefits*. 2008;1(8):26–33.
62. Saverno KR, Seal B, Goodman MJ, Meyer K. Economic evaluation of quality-of-life improvement with second-generation antihistamines and montelukast in patients with allergic rhinitis. *American Health and Drug Benefits*. 2009;2(7):309–15.
63. Tillement J-P, Testa B, Brée F. Compared pharmacological characteristics in humans of racemic cetirizine and levocetirizine, two histamine H1-receptor antagonists. *Biochemical Pharmacology*. 2003;66(7):1123–6.
64. Middleton E. *Allergy: Principles and Practice*. 5th ed. St. Louis: Mosby; 1998.
65. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: a consensus report. *Current Medical Research and Opinion*. 2004;20(12):1937–52.
66. Burton WN, Conti DJ, Chen CY, Schultz AB, Edington DW. The impact of allergies and allergy treatment on worker productivity. *Journal of Occupational and Environmental Medicine/American College of Occupational and Environmental Medicine*. 2001;43(1):64–71.
67. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices—modeling studies. *Value in Health*. 2003;6(1):9–17.
68. Bachert C, Bousquet J, Canonica GW, et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *The Journal of Allergy and Clinical Immunology*. 2004;114(4):838–44.