

# Drug Class Review

## Newer Antihistamines

Preliminary Scan Report 1  
Update 3

November 2012

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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 to assist with Participating Organizations' consideration of allocating resources toward a full report update, a single drug addendum, or a summary review. 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 US Food and Drug Administration since the last report. Other important studies could exist.

### Date of Last Update Report

Update 2, May 2010 (searches through December 2009)

### Date of Last Preliminary Update Scan Report

None since most recent update report

### Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The Participating Organizations of Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Participating Organizations approved the following key questions to guide this review:

Key question 1. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?

Key question 2. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in harms?

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), co-morbidities (drug-disease interactions), or pregnancy for which one newer antihistamine is more effective or associated with fewer harms?

### Inclusion Criteria

#### *Populations*

- Adult or pediatric outpatients with the following conditions:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Urticaria (acute and chronic)
- Subgroups of interest included, but were not limited to, different races, ages (older adult compared with younger adult), concomitant use of other medications (in consideration of drug-drug interactions), persons with various comorbidities (pregnancy and consideration of drug-disease interactions), and sex.

## Interventions

**Table 1. Included drugs and their labeled indications**

Drug	Trade name(s)	Labeled indications	Dosage form/Route
Cetirizine hydrochloride	Zyrtec <sup>®</sup>	SAR; PAR; Chronic Urticaria	Syrup/Oral
	Reactine <sup>®a</sup>	SAR <sup>b</sup> ; PAR; Chronic Urticaria <sup>c</sup>	Tablet; Chewable tablet; Syrup/Oral
Loratadine	Claritin <sup>®</sup>	SAR; PAR <sup>a</sup> ; Chronic Urticaria	Tablet; ODT <sup>a</sup> ; Syrup; Capsule <sup>d</sup> /Oral
Fexofenadine hydrochloride	Allegra <sup>®</sup>	SAR; PAR <sup>a</sup> ; Chronic Urticaria	Tablet; ODT; Suspension; Capsule <sup>a</sup> /Oral
Desloratadine	Clarinex <sup>®d</sup>	SAR; PAR; Chronic Urticaria	Tablet; ODT; Syrup/Oral
	Aerius <sup>®a</sup>	Allergic Rhinitis <sup>c</sup> ; SAR <sup>b</sup> ; Chronic Urticaria	Tablet; Syrup/Oral
Levocetirizine	Xyzal <sup>®d</sup>	SAR; PAR; Chronic Urticaria	Tablet; Solution/Oral
Azelastine	Astelin <sup>®d</sup>	SAR	Spray; Metered/Nasal
	Astepro <sup>®d</sup>	SAR; PAR	Spray; Metered/Nasal
Olopatadine	Patanase <sup>®d</sup>	SAR	Spray; Metered/Nasal

Abbreviations: ODT, orally disintegrating tablet; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.

<sup>a</sup> Only available in Canada.

<sup>b</sup> For children only.

<sup>c</sup> For adults only.

<sup>d</sup> Not available in Canada.

## Study designs

1. Efficacy and effectiveness
  - a. Randomized controlled trials, controlled clinical trials, and systematic reviews of fair or better quality.
  - b. Direct comparisons (head-to-head studies) were preferred over indirect comparisons using active or placebo-controlled trials. Inclusion of indirect evidence will be considered where there is insufficient direct evidence.
  - c. Studies  $\geq 1$  week in duration were included.
  - d. Studies conducted in artificial study settings (for example, antigen exposure chambers) were not be included. Abstracts and conference proceedings are also excluded.

## 2. Harms

- a. Randomized controlled trials, controlled clinical trials, pre-compared with post-design studies, and observational studies with comparative groups.
- b. To be included, reports about overall harms or adverse events had to report total withdrawals, withdrawals due to specific adverse events (for example, central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention, etc.), or the frequency and severity of these specific adverse events.

### **Outcomes**

The following were the primary outcomes for this review:

- Efficacy and effectiveness
  - Symptoms (nasal congestion, rhinorrhea, sneezing, itching and pain from skin irritations)
  - Functional capacity (physical, social and occupational functioning, quality of life)
  - Time to relief of symptoms (time to onset, duration of relief)
  - Duration of effectiveness (switch rate)
- Harms
  - Total withdrawals
  - Withdrawals due to adverse events
  - Serious adverse events or withdrawals due to specific adverse events (central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention)

## **METHODS**

### **Literature Search**

To identify relevant citations, we searched Ovid MEDLINE and Ovid MEDLINE In-Process & Other Non-Indexed Citations from December 2009 through November 2012 using terms for included drugs. We also searched the US Food and Drug Administration website (<http://www.fda.gov/medwatch/safety.htm>) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (<http://www.ahrq.gov/>) and the Canadian Agency for Drugs and Technology in Health (<http://www.cadth.ca/>). All citations were imported into an electronic database (EndNote X3) 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

### New Drugs

#### ***New drugs identified in this Preliminary Update Scan***

None.

#### ***New drugs identified in previous Preliminary Update Scan(s)***

No scan since most recent update report.

### New Indications

#### ***New indications identified in this Preliminary Update Scan***

None.

#### ***Identified in previous Preliminary Update Scan(s)***

No scan since most recent update report.

### Comparative Effectiveness Reviews

#### ***Reviews identified in this Preliminary Update Scan***

We identified a protocol of a potentially relevant comparative effectiveness review produced by the Agency for Healthcare Research and Quality Effective Health Care Program. See appendix A for the key questions that describe the scope of the project.

Treatments for Seasonal Allergic Rhinitis, published online March 8, 2012

[http://effectivehealthcare.ahrq.gov/ehc/products/376/1000/SAR\\_Protocol\\_20120308.pdf](http://effectivehealthcare.ahrq.gov/ehc/products/376/1000/SAR_Protocol_20120308.pdf)

#### ***Reviews identified in previous Preliminary Update Scan(s) <if relevant>***

No other scans since most recent update report.

### Randomized Controlled Trials

#### ***Trials identified since the most recent Full Report***

Medline searches resulted in 81 citations. Of those, there are 5 new potentially relevant head to head trials (see Appendix B for abstracts). Four out of 5 trials have levocetirizine as a treatment arm while 3 out of 5 trials have desloratadine as a treatment arm. There are three trials on allergic rhinitis and 2 on urticaria. Table 1 summarizes the populations and comparisons included in these studies. Titles and abstracts for these citations are also available in appendix B.

Additionally, there are 19 new placebo controlled trials identified in this scan most of which pertain to comparisons of levocetirizine and olopatadine to placebo. These trials would not be included in a Drug Effectiveness Review Project update if we were to create streamlined reports focusing on head to head trials only.

**Table 2. Characteristics of new head-to-head trials**

<b>Study</b>	<b>N, Duration</b>	<b>Population</b>	<b>Comparison</b>	<b>Focus</b>
Ciebiada, 2011	40, 32 weeks	Adults with allergic rhinitis	Montelukast, levocetirizine, desloratadine, montelukast+levocetirizine, montelukast+desloratadine	Symptom relief and score
LaForce, 2010	NR, 14 days	Patients ≥12 years of age with seasonal allergic rhinitis	Olopatadine nasal spray 0.6%+fluticasone nasal spray, Azelastine nasal spray 0.1%+fluticasone nasal spray	Symptom relief and scores, harms
Tzanetos, 2011	30, 3 months	Patients with perennial allergic rhinitis	Cetirizine 5 mg, Levocetirizine 5mg	Sedation
Hong, 2010 (no abstract)	NR	Chronic idiopathic urticaria	Desloratadine 5 mg, Levocetirizine 5 mg	NR
Staevska, 2010	80, NR	Adults with urticaria	Desloratadine max dose 20 mg, Levocetirizine max dose 20 mg	Symptom relief and scores, harms

## New Safety Alerts

### **Identified in this Preliminary Update Scan**

**Patanase**<sup>®</sup> (olopatadine hydrochloride) nasal spray: *as of February 2012*, the following labeling revision

#### WARNINGS AND PRECAUTIONS

##### ***Nasal Septal Perforation:***

- In the third safety trial, 1 patient exposed to the 3.7 pH vehicle nasal spray (containing no povidone) reported a nasal septal perforation.

**Xyzal**<sup>®</sup> (levocetirizine dihydrochloride) oral solution and tablets: *as of September 2012*, the following labeling revision

#### WARNINGS AND PRECAUTIONS

##### Urinary Retention

Urinary retention has been reported post-marketing.

### **Identified in previous Preliminary Update Scan(s)**

No scan since most recent update report.

## Summary and Recommendations

There are no new drugs and no new indications available for the newer antihistamines. Bilastine and Rupatadine are yet to receive US Food and Drug Administration approval. The volume and

nature of the head to head trials is not very compelling. The Evidence-based Practice Center is not recommending a new update or a summary review or an addendum at this time.

## **Appendix A. Systematic review produced by the Effective Health Care Program**

### **Treatments for Seasonal Allergic Rhinitis**

#### **The Key Questions**

##### **Question 1**

What is the comparative effectiveness of pharmacologic treatments, alone or in combination with each other, for adults and adolescents ( $\geq 12$  years of age) with mild or with moderate/severe seasonal allergic rhinitis (SAR)?

1. How does effectiveness vary with long-term (months) or short-term (weeks) use?
2. How does effectiveness vary with intermittent or continuous use?
3. For those with symptoms of allergic conjunctivitis, does pharmacologic treatment of SAR provide relief of eye symptoms (itching, tearing)?
4. For those codiagnosed with asthma, does pharmacologic treatment of SAR provide asthma symptom relief?

##### **Question 2**

What are the comparative adverse effects of pharmacologic treatments for SAR for adults and adolescents ( $\geq 12$  years of age)?

1. How do adverse effects vary with long-term (months) and short-term (weeks) use?
2. How do adverse effects vary with intermittent or continuous use?

##### **Question 3**

For the subpopulation of pregnant women, what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

1. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
2. How do effectiveness and adverse effects vary with intermittent or continuous use?

##### **Question 4**

For the subpopulation of children ( $< 12$  years of age), what are the comparative effectiveness and comparative adverse effects of pharmacologic treatments, alone or in combination with each other, for mild and for moderate/severe seasonal allergic rhinitis (SAR)?

1. How do effectiveness and adverse effects vary with long-term (months) or short-term (weeks) use?
2. How do effectiveness and adverse effects vary with intermittent or continuous use?



## Appendix B. Abstracts of potentially relevant new trials of Newer Antihistamines

Ciebiada, M., M. Gorska-Ciebiada, et al. (2011). "Use of montelukast alone or in combination with desloratadine or levocetirizine in patients with persistent allergic rhinitis." American Journal of Rhinology & Allergy **25**(1): e1-6.

**BACKGROUND:** We assessed the course of treatment in patients with persistent allergic rhinitis (AR) treated with montelukast, levocetirizine, or desloratadine alone or combinations of antihistamine and montelukast. **METHODS:** A 32-week randomized, double-blind, placebo-controlled, crossover, double-armed study in 40 adult patients with history of persistent AR, clinical allergy to house-dust mites, and a total nasal symptom score of at least 5 (congestion of at least 2) has been performed. Patients with asthma, chronic obstructive pulmonary disease, nonallergic rhinitis with clinical allergy associated with seasonal allergens, and other serious diseases were excluded. There were four 6-week treatment periods separated by 2-week washout periods. Twenty patients received either montelukast or antihistamine, a combination of montelukast and antihistamine, or placebo. The sequence of treatment was randomly assigned. Nasal symptoms were assessed using a 4-point scale at baseline, daily during the 1st week and on days 14, 21, 28, 35, and 42 of treatment. **RESULTS:** Montelukast alone, levocetirizine alone, desloratadine alone, and the montelukast/antihistamine combinations significantly improved nasal symptoms during the first 24 hours. Improvement gradually increased during the 6 weeks of treatment, especially in patients receiving montelukast alone or in combination therapy with the antihistamine in both arms. Improvement at 42 days of treatment was significantly greater than that achieved on the 1st day of therapy in patients treated with the combination of montelukast and levocetirizine. **CONCLUSION:** Montelukast alone or in combination with antihistamines gave a gradual increase in nasal symptom improvement within 6 weeks of treatment in patients with persistent AR.

Hong, J.-B., H.-C. Lee, et al. (2010). "A randomized, double-blind, active-controlled, parallel-group pilot study to compare the efficacy and sedative effects of desloratadine 5 mg with levocetirizine 5 mg in the treatment of chronic idiopathic urticaria." Journal of the American Academy of Dermatology **63**(5): e100-102.

LaForce, C. F., W. Carr, et al. (2010). "Evaluation of olopatadine hydrochloride nasal spray, 0.6%, used in combination with an intranasal corticosteroid in seasonal allergic rhinitis." Allergy & Asthma Proceedings **31**(2): 132-140.

The combination of intranasal antihistamines and intranasal corticosteroids results in superior relief of seasonal allergic rhinitis (SAR) symptoms compared with monotherapy. This study was designed to evaluate the safety and efficacy of olopatadine hydrochloride nasal spray, 0.6% (OLO), administered in combination with fluticasone nasal spray, 50 micrograms (FNS), relative to azelastine nasal spray, 0.1% (AZE), administered in combination with FNS in the treatment of

SAR. This was a multicenter, double-blind, randomized, parallel-group comparison of OLO + FNS versus AZE + FNS administered for 14 days to patients  $\geq$  12 years of age with histories of SAR. Efficacy assessments recorded by patients in a daily diary included nasal symptom scores. Safety was evaluated based on adverse events (AEs). Pretreatment values for reflective total nasal symptoms scores (rTNSS) were similar for both treatment groups. The mean (SD) 2-week average rTNSS was 4.28 (2.63) for OLO + FNS and 4.15 (2.63) for AZE + FNS; these scores were not statistically different between treatment groups. No significant differences ( $p > 0.05$ ) between OLO + FNS and AZE + FNS were observed for the average 2-week percent changes from baseline in rTNSS or in the individual nasal symptoms (nasal congestion, rhinorrhea, itchy nose, and sneezing). Compared with baseline, both groups had statistically significant improvement in rTNSS ( $p < 0.05$ ). No serious AEs were reported in either group during the study period. Overall, 19 AEs were reported in the OLO + FNS group and 29 AEs were reported in the AZE + FNS group. OLO, when administered adjunctively with FNS, is effective, safe, and well-tolerated in patients with SAR.

Staevska, M., T. A. Popov, et al. (2010). "The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria." Journal of Allergy & Clinical Immunology **125**(3): 676-682.

**BACKGROUND:** H(1)-antihistamines are first line treatment of chronic urticaria, but many patients do not get satisfactory relief with recommended doses. European guidelines recommend increased antihistamine doses of up to 4-fold. **OBJECTIVE:** To provide supportive evidence for the European guidelines. **METHODS:** Eighty tertiary referral patients with chronic urticaria (age range, 19-67 years) were randomized for double-blind treatment with levocetirizine or desloratadine (40/40). Treatment started at the conventional daily dose of 5 mg and then increased weekly to 10 mg, 20 mg, or 20 mg of the opposite drug if relief of symptoms was incomplete. Wheal and pruritus scores, quality of life, patient discomfort, somnolence, and safety were assessed. **RESULTS:** Thirteen patients became symptom-free at 5 mg (9 levocetirizine vs 4 desloratadine), compared with 28 subjects on the higher doses of 10 mg (8/7) and 20 mg (5/1). Of the 28 patients nonresponsive to 20 mg desloratadine, 7 became symptom-free with 20 mg levocetirizine. None of the 18 levocetirizine nonresponders benefited with 20 mg desloratadine. Increasing antihistamine doses improved quality of life but did not increase somnolence. Analysis of the effect of treatment on discomfort caused by urticaria showed great individual heterogeneity of antihistamine responsiveness: approximately 15% of patients were good responders, approximately 10% were nonresponders, and approximately 75% were responders to higher than conventional antihistamine doses. No serious or severe adverse effects warranting discontinuation of treatment occurred with either drug. **CONCLUSION:** Increasing the dosage of levocetirizine and desloratadine up to 4-fold improves chronic urticaria symptoms without compromising safety in approximately three quarters of patients with difficult-to-treat chronic urticaria.

Tzanetos, D. B., J. M. Fahrenholz, et al. (2011). "Comparison of the sedating effects of levocetirizine and cetirizine: a randomized, double-blind, placebo-controlled trial." Annals of Allergy, Asthma, & Immunology **107**(6): 517-522.

**BACKGROUND:** Compared with placebo, levocetirizine has been found to be less sedating than cetirizine in separate trials. However, whether levocetirizine is less sedating than its parent drug cetirizine has not yet been studied in a randomized trial. **OBJECTIVE:** To determine whether levocetirizine is less sedating than cetirizine. **METHODS:** We conducted a randomized, double-blind, crossover, placebo-controlled trial examining sedation and allergy symptoms in patients with perennial allergic rhinitis who had previously reported significant sedation with cetirizine. Enrollment ran from January 28, 2009, to February 25, 2009. All patients completed the study by April 17, 2009. Thirty patients enrolled, and 29 patients completed the study (1 patient did not return her questionnaire). In a double-blind fashion, the 29 study participants received levocetirizine, 5 mg daily for 1 week, cetirizine, 10 mg daily for 1 week, and an equivalent placebo pill for 1 week in randomized order with washout periods before each treatment arm. At the end of each washout period and each treatment period, participants completed a 1-page questionnaire. This questionnaire included questions about sedation or sleepiness in the form of a modified Epworth Sleepiness Scale, a Likert scale measuring general or global sedation, and allergy symptoms as measured by the total rhinitis symptom score. **RESULTS:** Sedation as measured by both the modified Epworth Sleepiness Scale and the Likert scale was not significantly different between the levocetirizine and cetirizine treatments. **CONCLUSIONS:** In patients with a perceived history of sedation with cetirizine, most were able to tolerate levocetirizine. However, this controlled trial also suggests that many of these patients would tolerate cetirizine if given in a masked manner. Therefore, patients with a history of mild to moderate sedation with cetirizine are unlikely to experience a different sedation profile with levocetirizine. Copyright Copyright 2011 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.