OPTUMRx

Therapeutic Class Overview
Antihistamines, Second Generation

INTRODUCTION

- Oral antihistamines have been a mainstay in the treatment of allergic rhinitis and chronic idiopathic urticaria (CIU) since their development in the first half of the 20th century *(Janssen 1993)*.
- Although first-generation antihistamines are effective at ameliorating symptoms associated with allergic rhinitis and CIU, use in practice is limited by their lack of selectivity for the histamine 1 (H_1)-receptor and their ability to cross the blood-brain barrier, both resulting in adverse effects. Second-generation antihistamines were developed to maintain the efficacy of the first-generation agents, while reducing associated adverse effects. Due to a more complex chemical structure, the movement of second-generation antihistamines across the blood-brain barrier is reduced. In addition to a safer adverse event profile, second-generation agents have a longer duration of action, which allows for once- or twice-daily dosing for most products *(Lehman et al 2006)*.
- Despite the efficacy of second-generation antihistamines for the treatment of allergic rhinitis, they are not effective in the treatment of nasal congestion *(Lehman et al 2006, Seidman et al 2015)*. Because of this, they are often combined with a decongestant. Second-generation antihistamines combined with pseudoephedrine have been shown to improve symptoms and quality of life in patients with allergic rhinitis and nasal congestion compared to antihistamines alone *(Seidman et al 2015)*.
- This review focuses on the use of the second-generation antihistamines for the treatment of CIU, perennial allergic rhinitis (PAR), and seasonal allergic rhinitis (SAR).
- Several products formerly available by prescription (Rx) are now available over-the-counter (OTC). This review includes Rx products and those that are sold both by Rx and OTC. Products sold solely OTC are not included in this review. However, the clinical efficacy section retains some information on OTC products that were formerly available by Rx for informational purposes.
- Medispan Class: Antihistamines – Non-Sedating and Cough/Cold/Allergy Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cetirizine*	
cetirizine oral solution/syrup (Rx/OTC)	√
OTC-only products include tablets, chewable tablets, liquid-filled capsules, and orally disintegrating tablets (ODT)	
Desloratadine	
Clarinex (desloratadine) oral solution/syrup (Rx only)	-†
Clarinex (desloratadine) tablet (Rx only)	√
desloratadine ODT (Rx only)	√
Fexofenadine*	
OTC-only products include tablets, oral suspension, and ODT	
Levocetirizine*	
levocetirizine tablet (Rx/OTC)	√
levocetirizine oral solution (Rx/OTC)	√
Loratadine*	
OTC-only products include tablets, capsules, chewable tablets, solution/syrup, and ODT	
Antihistamine – decongestant combinations*	
Clarinex-D 12 Hour (desloratadine/pseudoephedrine extended release tablet) (Rx only)	-
Clarinex-D 24 Hour (desloratadine/pseudoephedrine extended release tablet) (Rx only)‡	-†

Drug	Generic Availability
Semprex-D (acrivastine/pseudoephedrine capsule) (Rx only)	-
OTC-only combinations include fexofenadine/pseudoephedrine, loratadine/pseudoephedrine, and cetirizine/ pseudoephedrine extended release tablets	

*Medication or combination is available OTC in at least 1 dosage form or strength. OTC products are available in various brand and private label names.
†Generic product has been FDA-approved but is not currently marketed.
‡Clarinex-D 24 Hour is no longer marketed.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018, Facts and Comparisons 2018*)

INDICATIONS

Table 2a. FDA-Approved Indications – Single Entity Agents*

Indication	Cetirizine†	Desloratadine‡	Levocetirizine
CIU	√ (age 6 months to 5 years)	√ (ages 6 months and older)	√ (age 6 months and older)
PAR	√ (age 6 to 23 months)	√ (ages 6 months and older)	√ (age 6 months and older)
SAR		√ (ages 2 years and older)	√ (ages 2 years and older)

*The indications listed in the table are based on current prescription labeling. All OTC single entity products are to be used for the temporary relief of runny nose; sneezing; itchy, watery eyes; or itching of the nose and throat due to hay fever or other upper respiratory allergies.
†Oral solution indications (other formulations are no longer available by prescription)
‡The CIU indication is for the tablets and oral solution/syrup only; the ODT formulation is indicated for PAR and SAR, and is not recommend for use in patients ≤ 6 years of age because the oral solution is better suited for these patients.

(*Clinical Pharmacology 2018, Facts and Comparisons 2018, Prescribing information: Cetirizine 2016, Clarinex 2018, Desloratadine 2017, Levocetirizine 2018*)

Table 2b. FDA-Approved Indications – Combination Agents*

Indication	Acrivastine/pseudoephedrine	Desloratadine/pseudoephedrine
Relief of symptoms of SAR, including nasal congestion, in adults and adolescents aged ≥ 12 years	√	√

*The indication listed in the table is based on current prescription labeling. All OTC combination agents are to be used for the temporary relief of runny nose; sneezing; itchy, watery eyes; or itching of the nose and throat due to hay fever or other upper respiratory allergies; they also temporarily relieve nasal congestion and reduce nasal passage swelling.

(*Clinical Pharmacology 2018, Facts and Comparisons 2018, Prescribing information: Clarinex-D [12 hour] 2018, Semprex-D 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials have demonstrated that second-generation antihistamines are more effective in treating and providing symptomatic relief of CIU, PAR, and SAR compared to placebo *(Kaplan et al 2005, Kapp et al 2006, Kim et al 2006, Monroe et al 2003, Nathan et al 2006, Nayak et al 2017, Nettis et al 2006, Potter et al 2003, Potter et al 2005, Okubo et al 2005, Ring et al 2001, Simons et al 2003)*.
- When agents within the class were compared, one agent did not consistently demonstrate greater efficacy over another *(Anuradha et al 2010, Boyle et al 2005, Ciprandi et al 2005, Day et al 1998, Day et al 2001, Day et al 2004, Garg et al 2007, Handa et al 2004, Lee et al 2009, Meltzer et al 1996, Nayak et al 2017, Potter et al 2009, Prenner et al 2000, Purohit et al 2004, Van Cauwenberge et al 2000)*.
- In a systematic review by Benninger et al, second-generation antihistamines were associated with a 23.5% reduction from baseline in total nasal symptom scores for SAR, and a 51.4% reduction in symptoms of PAR. Although intranasal

corticosteroids were more effective for SAR (40.7% reduction), they were not as effective as long-term oral antihistamines in patients with PAR (37.3% reduction) (*Benninger et al 2010*).

- In a comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ), oral selective antihistamines were equivalent to montelukast for nasal and eye symptoms in patients with SAR. Based on evidence of safety, in order to avoid insomnia, an oral selective antihistamine was preferred over the combination of an oral selective antihistamine with a decongestant or monotherapy with a decongestant *(Glacy et al 2013)*.
- In a systematic review of 73 randomized controlled trials in CIU, at standard treatment doses, the second-generation antihistamines were effective when compared with placebo. Cetirizine 10 mg once daily in the short term and in the intermediate term was effective in completely suppressing urticaria. Evidence was limited for desloratadine given at 5 mg once daily in the intermediate term and at 20 mg in the short term. Levocetirizine at 5 mg was effective for complete suppression in the intermediate term but not in the short term. No single agent was demonstrated to be more effective than another, and there is a lack of available head-to-head trials *(Sharma et al 2014)*.

CLINICAL GUIDELINES

- According to the current clinical guidelines for the management of allergic rhinitis, intranasal corticosteroids should be considered first-line therapy in the majority of patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis. Although intranasal corticosteroids are the most effective drugs for treating allergic rhinitis, second-generation antihistamines may be used in patients with mild-to-moderate disease, especially those with a preference for oral therapy and with complaints of sneezing and itching. Considering their safety profile, second-generation antihistamines should be considered as first-line symptomatic treatment for urticaria *(Bernstein et al 2014, Brozek et al 2017, Dykewicz et al 2017, Grattan et al 2007, Seidman et al 2015, Wallace et al 2008, Zuberbier et al 2014)*.

SAFETY SUMMARY

- Levocetirizine is contraindicated in patients with severe renal impairment and in pediatric patients 6 months to 11 years of age with impaired renal function.
- Due to the pseudoephedrine component, the combination agents are contraindicated in patients with narrow angle glaucoma, severe hypertension or coronary artery disease, or urinary retention. The combination agents should not be used when there has been treatment with a monoamine oxidase inhibitor within the last 14 days.
- The most common adverse effects are associated with sedation and fatigue.

DOSING AND ADMINISTRATION

- For the combination agents, at least 14 days must elapse after discontinuation of a monoamine oxidase inhibitor before starting treatment.
- Extended-release products should be swallowed whole; tablets should not be broken, chewed, or crushed.

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Single Entity Agents			
Cetirizine	Oral	Once or twice daily	Dosage adjustment in renal and hepatic impairment is required.
Desloratadine	Oral	Once daily	Dosage adjustment in renal and hepatic impairment is required.
Levocetirizine	Oral	Once daily in the evening	Dosage adjustment in renal impairment is required.
Combination Agents			
Acrivastine/ pseudoephedrine	Oral	4 times per day	Avoid use in patients with creatinine clearance ≤ 48 mL/minute.
Desloratadine/ pseudoephedrine	Oral	Once or twice daily (the once-daily product is not currently marketed)	Avoid use in patients with renal and hepatic impairment (combination product was not studied in these populations).

See the current prescribing information for full details.

CONCLUSION

- Second-generation antihistamines have been shown to significantly improve the symptoms of allergic rhinitis and CIU, without the unwanted adverse effects associated with the first-generation agents *(Sur et al 2010)*.
- Currently, all of the single entity second-generation antihistamines are available as generics and/or OTC in at least 1 dosage form. Cetirizine, fexofenadine, levocetirizine, and loratadine can be purchased OTC, and several different dosage forms are available for the OTC products *(Clinical Pharmacology 2018, Facts and Comparisons 2018, Micromedex 2018)*.
- Current evidence supports the use of second-generation antihistamines in the treatment of seasonal and perennial allergic rhinitis as well as CIU. In a systematic review by Benninger et al, second-generation antihistamines were associated with a 23.5% reduction from baseline in total nasal symptom scores for SAR, and a 51.4% reduction in symptoms of PAR *(Benninger et al 2010)*.
- Overall, clinical trials have not consistently demonstrated one single-entity second generation antihistamine agent to be more efficacious or safe than the others. Furthermore, there is a lack of head-to-head trials comparing the combination second generation antihistamine products, rendering a comparison of the agents difficult.
- Current consensus guidelines are consistent among organizations that antihistamines are somewhat less effective than intranasal corticosteroids, but may be used on a daily or as-needed basis. Second-generation antihistamines are recommended as they are less sedating and cause less central nervous system impairment compared to first-generation agents. Oral decongestants can be a useful addition to antihistamines in the treatment of nasal congestion *(Brozek et al 2017, Dykewicz et al 2017, Seidman et al 2015)*.
- Considering their efficacy and safety profile, second-generation antihistamines should be considered as first-line symptomatic treatment of urticaria. Additionally, patients should be offered the choice of at least 2 nonsedating antihistamines as response varies among individuals *(Bernstein et al 2014, Grattan et al 2007, Zuberbier et al 2014)*.

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