Therapeutic Class Overview
Intranasal Antihistamines

INTRODUCTION

- Allergic rhinitis is a condition characterized by nasal congestion, rhinorrhea, sneezing, itching of the nose, and/or postnasal drainage. Symptoms may also include pruritus of the eyes, palate, and ears (Snellman et al, 2013).
- Allergic rhinitis is common, affecting 10% to 30% of children and adults in the United States (U.S.) and other industrialized countries (Brozek et al, 2010; Wallace et al, 2008). Allergic rhinitis is also referred to in terms of the cyclical or persistent nature of symptoms. Seasonal allergic rhinitis (SAR) is that which occurs at a particular time of the year, whereas perennial allergic rhinitis (PAR) symptoms are present year round.
- Known risks factors for developing allergic rhinitis include family history of atopy, male sex, birth during the pollen season, firstborn status, early use of antibiotics, maternal smoking exposure in the first year of life, exposure to indoor allergens (e.g., dust mite allergen), serum immunoglobulin E (IgE) level >100 IU/mL before 6 years of age, and presence of allergen-specific IgE (Wallace et al, 2008).
- Allergic rhinitis may be classified by its intermittent or persistent pattern and by severity (mild or moderate-severe). Intermittent patterns involve the presence of symptoms for less than 4 days per week or for less than 4 weeks; whereas persistent patterns entail the presence of symptoms more than 4 days per week and for more than 4 weeks (Brozek et al, 2010).
- Mild disease is classified as the presence of symptoms without the presence of sleep disturbances; impairment in school or work performance; impairment in daily activities, leisure and/or sport activities; or troublesome symptoms. If one or more of these complications are present, the condition is considered moderate-severe in nature (Brozek et al, 2010).
- Treatment goals involve resolving symptoms, minimizing morbidity, preventing disease progression, improving the individual's quality of life, minimizing adverse drug events, reducing direct and indirect economic costs associated with disease progression and loss of productivity (e.g., missed work or school days), and ensuring the appropriate step-wise approach of drug therapy to utilize targeted therapies specific to symptomatology and reduce unnecessary healthcare spending (Brozek et al, 2010).
- Non-pharmacologic approaches to preventing and managing the symptoms of allergic rhinitis include allergen avoidance (dust mites, animal dander, mold, and smoke exposure, etc.), nasal saline irrigation, exclusive breastfeeding for at least the first 3 months for all infants irrespective of the family history of atopy, as well as multifaceted interventions to reduce early life exposure to house dust mites (e.g., bed encasings, hard wood flooring vs carpeting, washing bedding in temperatures exceeding 55°C [131°F]) (Brozek et al, 2010; Wallace et al, 2008).
- Pharmacological approaches to managing allergic rhinitis include single-entity and combination agents from the following classes of medications: intranasal antihistamines, intranasal corticosteroids, intranasal cromolyn, intranasal ipratropium, oral non-sedating antihistamines, decongestants, leukotriene receptor antagonists, oral glucocorticoids, immunotherapy, and ocular administration of medications for ocular symptoms, when present (Brozek et al, 2010; Snellman et al, 2013; Wallace et al, 2008).
- This review will focus on the intranasal antihistamines, which include azelastine, olopatadine, and the combination of an intranasal antihistamine with a corticosteroid, azelastine/fluticasone propionate. Azelastine and olopatadine are H_1-receptor antagonists, which block the activity of histamine to relieve the symptoms of allergic rhinitis (Prescribing information: ASTELIN®, 2014; ASTEPRO®, 2015).
- DYMISTA® is a product combining the antihistaminergic activity of azelastine with the effects of the glucocorticoid, fluticasone propionate. The mechanism of action of glucocorticoids is multifactorial in the management of allergic rhinitis. Although the precise mechanism of fluticasone propionate is unknown, this class of agents has been shown to have varying effects on multiple types of cells, including mast cells, eosinophils, neutrophils, macrophages, and lymphocytes; as well as other inflammatory mediators such as histamine, eicosanoids, leukotrienes, and cytokines (DYMISTA prescribing information, 2015). Another combination product, TICALAST® (azelastine/fluticasone propionate) nasal kit, is no longer marketed per the manufacturer, Shoreline Pharmaceuticals, Inc.
- Medispan Classes: Nasal Antiallergy and Nasal Agent Combination

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ASTELIN* (azelastine hydrochloride) nasal solution, 137 µg	Mylan Pharmaceuticals, Inc.	11/01/1996	√
ASTEPRO* (azelastine hydrochloride) nasal solution, 0.15% (205.5 µg)	Mylan Pharmaceuticals, Inc.	08/31/2009	√
DYMISTA (azelastine hydrochloride/ fluticasone propionate) nasal suspension, 137 µg/50 µg	Mylan Pharmaceuticals, Inc.	05/01/2012	√†
PATANASE® (olopatadine hydrochloride) nasal solution, 0.6%	Alcon Laboratories, Inc.	04/15/2008	√

*In August 2016, Mylan Pharmaceuticals completed the acquisition of Meda Pharmaceutical products, including branded ASTELIN, ASTEPRO, and DYMISTA. After the acquisition, certain products were no longer marketed including the branded agent ASTELIN and the ASTEPRO 0.1% nasal solution; although, these products are available generically.
†Generic product manufactured by Apotex Inc. was FDA-approved on April 28, 2017 but is not yet on the market.

(DRUGS@FDA, 2017; Mylan Pharmaceuticals press release, 2016)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	ASTELIN	ASTEPRO	DYMISTA	PATANASE
Treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in adults and children 5 years and older	√	-	-	-
Treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip in adults and children 12 years and older	√	-	-	-
Relief of the symptoms of seasonal and perennial allergic rhinitis in patients 6 years of age and older	-	√	-	-
Relief of symptoms of seasonal allergic rhinitis in patients 6 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief	-	-	√	-
Relief of the symptoms of seasonal allergic rhinitis in adults and children 6 years of age and older	-	-	-	√
Relief of the symptoms of seasonal allergic rhinitis in adults and children 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older	-	√	-	-

(Prescribing information: ASTELIN, 2014; ASTEPRO, 2015; DYMISTA, 2015; PATANASE, 2015)

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

CLINICAL EFFICACY SUMMARY

- Intranasal azelastine has been shown to be safe and effective over 14 days of treatment in placebo-controlled trials (Howland et al, 2011; Lumry et al, 2007; van Bavel et al, 2009).
- When ASTELIN 0.1% and ASTEPRO 0.15% were compared to placebo in a 2-week trial, there was a significantly greater improvement in total nasal symptom score (TNSS) for both ASTEPRO and ASTELIN vs. placebo (P<0.001). In a retrospective analysis, there was a statistical difference in favor of ASTEPRO 0.15% compared to ASTELIN 0.1% (P=0.047) (Shah et al, 2009[a]).
- A meta-analysis compared azelastine hydrochloride nasal spray to other agents used in the management of SAR and PAR which included beclomethasone nasal spray and loratadine combination, terfenadine (not available in the U.S.), oral cetirizine, budesonide nasal spray, ebastine (not available in the U.S.), levocabastine (not available in the U.S) and oral loratadine. The analysis did not identify a statistically significant difference in treatment response, despite multiple analyses. For TNSS, azelastine was more efficacious compared to placebo (effect size, 0.36; 95% confidence interval [CI], 0.26 to 0.46) (Lee et al, 2007).
- The combination of azelastine hydrochloride with fluticasone propionate nasal spray was significantly more effective compared to the individual agents in various symptom scores in a 2-week, multicenter, double-blind, randomized trial. The improvement in TNSS score from baseline was 37.9% for combination therapy compared to 27.1% and 24.8%, respectively, with single-entity fluticasone and azelastine (P<0.05 for the combination vs either agent alone) (Ratner et al, 2008).
- Other randomized trials comparing the combination of azelastine hydrochloride nasal spray and fluticasone propionate nasal spray have also demonstrated significant improvements in TNSS, individual symptom scores, and quality of life ratings compared to each agent administered as monotherapy (Carr et al, 2012; Hampel et al, 2010; Meltzer et al, 2012).
- In addition, a randomized, active-controlled, open-label study demonstrated that long-term treatment with combination azelastine hydrochloride and fluticasone propionate nasal spray was well-tolerated (Berger et al, 2014).
- A meta-analysis evaluated combination azelastine hydrochloride and fluticasone propionate nasal spray, sublingual allergen immunotherapy (SLIT), second generation H1-antihistamines, nasal corticosteroids, and montelukast for the treatment of SAR. By indirect comparison, grass pollen SLIT tablets had a greater relative clinical impact compared to azelastine hydrochloride and fluticasone propionate nasal spray, second generation H1-antihistamines, and montelukast, and had a similar relative clinical impact as nasal corticosteroids (Devillier et al, 2014).
- Intranasal olopatadine has been proven safe and effective in placebo-controlled trials across a wide range of doses (Fairchild et al, 2007; Hampel et al, 2006; Meltzer et al, 2005; Meltzer et al, 2011; Patel et al, 2007; Ratner et al, 2005).
- Head-to-head studies have not demonstrated any statistically significant differences in efficacy between olopatadine hydrochloride and azelastine hydrochloride (Lieberman et al, 2011; Meltzer et al, 2008; Shah et al, 2009[b]).
- In a single-dose crossover study comparing ASTELIN with PATANASE, 60.6% of patients favored PATANASE, 30.3% favored ASTELIN, and 9.2% had no preference. Mean patient preference was significantly greater with PATANASE than ASTELIN for overall aftertaste, overall preference, and likelihood of use (Meltzer et al, 2008).
- Both ASTELIN and PATANASE significantly reduced vasomotor rhinitis symptom scores from baseline in a 2-week clinical trial; however, the difference between treatments was not statistically significant (Lieberman et al, 2011).
- In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of pharmacological therapies for the treatment of SAR. A total of 59 randomized controlled trials were selected to compare agents of 6 classes (oral and nasal antihistamines and decongestants, intranasal corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline) for relative efficacy. Overall, there was insufficient evidence to draw a conclusion about relative efficacy among most of the agents used for the treatment of SAR. For a few comparisons, sufficient evidence was available to draw a conclusion. Oral selective antihistamines and montelukast were equivalent for efficacy in reducing nasal and eye symptoms. Montelukast was superior to oral selective antihistamines for controlling asthma symptoms. Based on the evidence, intranasal antihistamines and intranasal corticosteroids had equivalent efficacy for nasal and eye symptoms. Similarly, montelukast was comparable to intranasal corticosteroids for nasal symptoms. The combination of intranasal antihistamines and intranasal corticosteroids demonstrated equivalent efficacy in

nasal and eye symptom resolution compared to either monotherapy. There is a paucity of information about the use of agents for the treatment of SAR in pregnant women. For children, conclusions about relative efficacy were not determined due to insufficient evidence (Glacy et al, 2013).
- Guidelines are summarized in the conclusion section of this document.

SAFETY SUMMARY

- There is a warning of central nervous system impairment requiring caution in performing tasks that require mental alertness associated with azelastine hydrochloride.
- Nasal ulcerations, epistaxis, and nasal septal perforation are potential concerns with the use of DYMISTA and PATANASE.
- Since DYMISTA is a combination product containing fluticasone propionate, safety concerns related to corticosteroids exist, including reduction in growth velocity, hypothalamus-pituitary-adrenal axis effects, immunosuppression, localized infections, glaucoma and/or cataract development, as well as drug interactions with concomitant use of agents known to be strong CYP 450 3A4 inhibitors (e.g., ritonavir, ketoconazole, etc.) due to the potential for increased adverse events.
- The most commonly reported adverse events associated with the intranasal antihistamines include headache, epistaxis, bitter taste, nasal discomfort, congestion, and ulcerations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose	Administration Considerations
ASTELIN (azelastine hydrochloride)	Nasal solution: 137 µg per spray (0.1%)	Treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in adults: One or 2 sprays per nostril twice daily. Treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip in adults: Two sprays per nostril twice daily.	Treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, sneezing, and nasal pruritus in children 5 to 11 years: One spray per nostril twice daily. Treatment of the symptoms of vasomotor rhinitis, such as rhinorrhea, nasal congestion, and postnasal drip in children 12 years and older: Two sprays per nostril twice daily.	Before initial use, the system should be primed with 4 sprays or until a fine mist appears. When 3 or more days have elapsed without use, the system should be primed with 2 sprays or until a fine mist appears.
ASTEPRO (azelastine hydrochloride)	Nasal solution: 205.5 µg per spray (0.15%)	Relief of the symptoms of seasonal allergic rhinitis in adults (0.1%, 0.15%): One or 2 sprays per nostril twice daily; or for 0.15% only, 2 sprays per nostril once daily. Relief of the symptoms of perennial allergic rhinitis in adults (0.1%, 0.15%): Two sprays per nostril twice daily.	Relief of the symptoms of seasonal allergic rhinitis in children 12 years and older (0.1%, 0.15%): One or 2 sprays per nostril twice daily; or 2 sprays per nostril once daily. Relief of the symptoms of perennial allergic rhinitis in children 12 years and older (0.1%, 0.15%): Two sprays per nostril twice daily.	Before initial use, the system should be primed with 6 sprays or until a fine mist appears. When 3 or more days have elapsed without use, the system should be primed with 2 sprays or until a fine mist appears.

Drug	Dosage Form: Strength	Recommended Adult Dose	Recommended Pediatric Dose	Administration Considerations
			Relief of symptoms of seasonal allergic rhinitis in children 6 to 11 years (0.1%, 0.15%): One spray per nostril twice daily. Relief of symptoms of perennial allergic rhinitis in children 6 to 11 years (0.1%, 0.15%): One spray per nostril twice daily. Relief of symptoms of seasonal allergic rhinitis in children 2 to 5 years (0.1%): One spray per nostril twice daily. Relief of symptoms of perennial allergic rhinitis in children 6 months to 5 years (0.1%): One spray per nostril twice daily.	
DYMISTA (azelastine hydrochloride/ fluticasone propionate)	Nasal suspension: 137 µg/50 µg per spray	Relief of symptoms of seasonal allergic rhinitis in adults who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief: One spray per nostril twice daily.	Relief of symptoms of seasonal allergic rhinitis in children 6 years and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief: One spray per nostril twice daily.	Before initial use, the system should be primed with 6 sprays or until a fine mist appears. When 14 or more days have elapsed without use, the system should be primed with one spray or until a fine mist appears.
PATANASE (olopatadine hydrochloride)	Nasal solution: 665 µg per spray (0.6%)	Relief of the symptoms of seasonal allergic rhinitis in adults: Two sprays per nostril twice daily.	Relief of the symptoms of seasonal allergic rhinitis in children 12 years and older: Two sprays per nostril twice daily. Relief of the symptoms of seasonal allergic rhinitis in children 6 to 11 years: One spray per nostril twice daily.	Before initial use, the system should be primed with 5 sprays or until a fine mist appears. When 7 or more days have elapsed without use, the system should be primed with 2 sprays or until a fine mist appears.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
ASTELIN (azelastine hydrochloride)	Start at the lower end of the dosing range.	Safety and effectiveness have not been established in children less than 5 years of age.	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
ASTEPRO (azelastine hydrochloride)	Clinical trials did not include a sufficient number of elderly to determine whether they respond differently than younger patients.	Safety and effectiveness have not been established in children less than 6 months of age.	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
DYMISTA (azelastine hydrochloride/ fluticasone propionate)	Start at the lower end of the dosing range.	Effectiveness has not been established in children less than 6 years of age, and safety has not been established in patients less than 4 years of age.†	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
PATANASE (olopatadine hydrochloride)	No dose adjustment required.	Safety and effectiveness have not been established in children less than 6 years of age.‡	No dose adjustment required.	No dose adjustment required.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

***** Pregnancy Category C=Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

† The safety of DYMISTA in children 4 to 5 years of age was similar to children 6 to 11 years of age, but efficacy was not established in 4 to 5 year olds.

CONCLUSION

- Allergic rhinitis is a common condition associated with significant morbidity and economic impact, affecting 10 to 30% of children and adults in the U.S. (Wallace et al, 2008).
- This condition is classified according to the severity of symptoms as well as its intermittent or persistent pattern of symptom occurrence (Brozek et al, 2010).
- Consensus guidelines offer multiple treatment options and do not offer a precise step-therapy approach for treating allergic rhinitis (Brozek et al, 2010; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).
- Intranasal antihistamines may be more effective than oral antihistamines for treatment of nasal symptoms, specifically for nasal congestion (Seidman et al, 2015).

- Intranasal antihistamines are effective therapies for managing the symptoms of allergic rhinitis; however, intranasal corticosteroids are generally recognized as the most effective single agents for controlling the broad spectrum of allergic rhinitis symptoms and are considered a first-line therapy in patients with moderate to severe symptoms. Intranasal antihistamines are an effective alternative to intranasal corticosteroids and have a faster onset of action than intranasal corticosteroids (Brozek et al, 2010; Glacy et al, 2013; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).
- The intranasal antihistamines are all considered equally effective treatment options in the management of allergic and vasomotor rhinitis, with no general preference given to one agent over another (Brozek et al, 2010; Seidman et al, 2015; Snellman et al, 2013; Wallace et al, 2008).
- The overall safety profile of the single-entity, intranasal antihistamines are comparable and all are generally well tolerated.
- ASTELIN is approved for children as young as 5 years old. ASTEPRO 0.15% and PATANASE are approved for use in children as young as 6 years of age. ASTEPRO 0.1% is approved for use in children as young as 6 months of age depending on the indication. DYMISTA is approved in children as young as 6 years of age.
- DYMISTA (azelastine hydrochloride/fluticasone propionate) is a combination product that utilizes both an intranasal antihistamine and an intranasal corticosteroid to manage the symptoms of allergic rhinitis.

REFERENCES

- ASTELIN® prescribing information. Meda Pharmaceuticals, Inc.; Somerset, NJ. October 2014.
- ASTEPRO® prescribing information. Meda Pharmaceuticals, Inc.; Somerset, NJ. February 2015.
- Berger WE, Shah S, Lieberman, et al. Long-term randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone in an advanced delivery system) in subjects with chronic rhinitis. J Allergy Clin Immunol Pract. 2014; 21:179-85.
- Brozek J, Bousquet J, Baena-Cagnani C, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466-76.
- Carr W, Bernstein J, Lieberman P, et al. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. J Allergy Clin Immunol. 2012 May;129(5):1282-1289.e10. doi: 10.1016/j.jaci.2012.01.077.
- Devillier P, Dreyfus JF, Demoly P, et al. A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. BMC Medicine. 2014, 12:71. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4101870/. Accessed May 16, 2017.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm Accessed May 16, 2017.
- DYMISTA® prescribing information. Meda Pharmaceuticals, Inc.; Somerset, NJ. February 2015.
- Fairchild C, Meltzer E, Roland P. Comprehensive report of the efficacy, safety, quality of life, and work impact of olopatadine 0.6% and olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2007;28:716-23.
- Glacy J, Putnam K, Godfrey S, et al. Treatments for Seasonal Allergic Rhinitis. Comparative Effectiveness Review No. 120. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 13-EHC098-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed May 16, 2017.
- Hampel FC, Ratner PH, Amar NJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCL nasal spray 0.4% and olopatadine HCL nasal spray 0.6% compared to vehicle placebo. Allergy and Asthma Proceedings. 2006;27:202-7.
- Hampel FC, Ratner PH, Van Bavel J, et al. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Ann Allergy Asthma Immunol. 2010 Aug;105(2):168-73. doi: 10.1016/j.anai.2010.06.008.
- Howland WC, Amar NJ, Wheeler W, et al. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in patients with allergy to Texas mountain cedar pollen. Int Forum Allergy Rhinol. 2011 Jul-Aug;1(4):275-9.
- Lee TA, Pickard AS. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. Pharmacotherapy. 2007;27(6):852-9.
- Lieberman P, Meltzer EO, LaForce CF, et al. Two-week comparison study of olopatadine hydrochloride nasal spray 0.6% vs azelastine hydrochloride nasal spray 0.1% in patients with vasomotor rhinitis. Allergy Asthma Proc. 2011 Mar-Apr;32(2):151-8.
- Lumry W, Prenner B, Corren J, et al. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. Ann Allergy Asthma Immunol. 2007;99:267-72.
- Meltzer EO, Blaiss M, Fairchild CJ. Comprehensive report of olopatadine 0.6% nasal spray as treatment for children with seasonal allergic rhinitis. Allergy Asthma Proc. 2011 May-Jun;32(3):213-20.
- Meltzer EO, Garadi R, LaForce C, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. Allergy Asthma Proc. 2008;29:659-68.
- Meltzer EO, Hampel FC, Rater PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. Annals of Allergy and Asthma Immunology. 2005;95:600-6.
- Meltzer EO, LaForce C, Ratner P, et al. MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: A randomized, double-blind, placebo-controlled trial of efficacy and safety. Allergy Asthma Proc. 2012 Jul;33(4):324-32.
- Mylan Pharmaceutical press release. Mylan Completes Acquisition of Meda. Website. August 5, 2016. Available at: http://newsroom.mylan.com/2016-08-05-Mylan-Completes-Acquisition-of-Meda. Accessed May 24, 2017.
- PATANASE® prescribing information. Alcon Laboratories, Inc.; Fort Worth, TX. October 2015.
- Patel P, Roland PS, Marple BF, et al. An assessment of the onset and duration of action of olopatadine nasal spray. Otolaryngology-Head and Neck Surgery. 2007;137:918-24.

- Ratner PH, Hampel F, Van Bravel J, et al. Combination therapy with azelastine hydrochloride nasal spray in the treatment of patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100:74-81.
- Ratner PH, Hampel FC, Amar NJ, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. Annals of Allergy, Asthma, & Immunology. 2005;95(5):474-9.
- Seidman MD, Gurgel RK, Lin ST, et al. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152(1 Suppl):SI-S43.
- Shah S, Berger W, Lumry W, et al. Efficacy and safety of azelastine 0.15% nasal spray and azelastine 0.10% nasal spray in patients with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009[a];30(6):628-33.
- Shah S, Nayak A, Ratner P, et al. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. Clin Ther. 2009[b];31(1):99-107.
- Snellman L, Adams W, Anderson G, et al. Diagnosis and Treatment of Respiratory Illness in Children and Adults (Fourth edition; 2013 January). Institute for Clinical Systems Improvement. Available at: https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_respiratory_guidelines/respiratory_illness/. Accessed May 16, 2017.
- van Bavel J, Howland W, Amar NJ, et al. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. Allergy and Asthma Proceedings. 2009;30(5):512-18.
- Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: An updated practice parameter of the joint task force on practice parameters for allergy and immunology. J Allergy Clin Immunol. 2008;122:S1-S84.

Publication Date: May 25, 2017