Therapeutic Class Overview
Intranasal Corticosteroids

INTRODUCTION

- Intranasal corticosteroids are primarily used to treat perennial allergic rhinitis (PAR) and seasonal allergic rhinitis (SAR) and may be useful in the treatment of some forms of nonallergic rhinitis (Wallace et al, 2008).
- Symptoms associated with allergic rhinitis include nasal congestion, rhinorrhea, sneezing and/or nasal itching. These symptoms result from a complex allergen-driven mucosal inflammation caused by resident and infiltrating inflammatory cells and a number of vasoactive and proinflammatory mediators (Dykewicz et al, 2017; Wallace et al, 2008).
- Treatment should consist of patient education, allergen avoidance activities and pharmacological therapies. Patients should be educated on how to avoid known triggers, such as aeroallergens, dust mites, molds and irritants whenever possible. In addition to environmental control measures, pharmacological therapies may be used to control symptoms.
- Intranasal corticosteroids down-regulate the inflammatory response by binding to the intracellular glucocorticoid receptors of inflammatory cells and causing a conformational change, thereby controlling the rate of protein synthesis and suppressing the transcription of cytokine and chemokine genes (Clinical Pharmacology®, 2017).
- Most intranasal corticosteroids are approved by the Food and Drug Administration (FDA) for the treatment of PAR and SAR. Mometasone (Nasonex) carries an additional indication for the prophylaxis of SAR. Nasacort Allergy 24hr (triamcinolone acetate), Flonase Allergy Relief (fluticasone propionate), Flonase Sensimist Allergy Relief (fluticasone furoate), and Rhinocort Allergy (budesonide) are all FDA-approved for over-the-counter use (Drugs@FDA, 2017).
- Nasal polyposis is an inflammatory condition of the nasal and sinus mucosa and usually presents as persistent nasal obstruction (Wallace et al, 2008). 2 currently available intranasal corticosteroids, beclomethasone (BECONASE AQ®) and mometasone (Nasonex) are also FDA-approved for the management of nasal polyps. In September 2017, fluticasone propionate (Xhance) was approved for management of nasal polyps in (Xhance prescribing information, 2017; Optinose press release, 2017).
- Beclomethasone (Beconase AQ) and fluticasone propionate are approved for the management of nonallergic rhinitis (eg, infectious rhinitis, hormonal rhinitis and vasomotor nonallergic rhinitis with eosinophilia syndrome). Unlike allergic rhinitis, nonallergic rhinitis is characterized by periodic or perennial symptoms that are not a result of immunoglobulin E-dependent events (Wallace et al, 2008).
- Beclomethasone (Qnasl) and ciclesonide (Zetonna) are the only 2 intranasal corticosteroid products formulated as a “dry” nasal aerosol; all other products within the class are formulated as aqueous suspensions.
- Recently, Veramyst (fluticasone furoate) was withdrawn from the market after over-the-counter Flonase Sensimist Allergy Relief (fluticasone furoate) was launched (GlaxoSmithKline press release, 2017; Snyder-Bulik, 2017). In January 2016, branded prescription Rhinocort Aqua was discontinued for the US market and over-the-counter Rhinocort Allergy spray was launched instead (AstraZeneca oral communication, 2017). Additionally, the prescription intranasal triamcinolone is unavailable per the FDA Orange Book, but the over-the-counter Nasacort Allergy 24hr spray is available (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- Continuous administration of intranasal corticosteroids is more efficacious than as-needed dosing, and the onset of therapeutic effect occurs between 3 and twelve hours (Dykewicz et al, 2017; Wallace et al, 2008).
- As a result of both the route of administration and the relatively low systemic bioavailability of these agents, intranasal corticosteroids are generally not associated with any clinically significant systemic adverse events. Moreover, drug interactions are limited when administered at recommended doses. The most common adverse events include nasal irritation and mild epistaxis.
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.
- Medispan Class: Nasal Steroids

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Beconase AQ (beclomethasone dipropionate monohydrate)	-
Flonase Allergy Relief† (fluticasone propionate)	✔

Drug	Generic Availability
Flonase Sesimist Allergy Relief† (fluticasone furoate)	-
flunisolide*	✔
fluticasone propionate*	✔
Nasacort Allergy 24hr† (triamcinolone acetonide)	✔
Nasonex (mometasone furoate monohydrate)	✔
Omnaris (ciclesonide)	-
Qnasl (beclomethasone dipropionate)	-
Rhinocort Allergy†‡ (budesonide)	✔
triamcinolone	✔
Xhance (fluticasone propionate)	-
Zetonna (ciclesonide)	-

*Brand prescription Flonase (fluticasone propionate), Nasalide (flunisolide), and Nasacort AQ (triamcinolone) are no longer marketed; however, generics for these products are available.
†Over-the-counter product
‡As of January 2016, AstraZeneca no longer produced for the US market branded prescription Rhinocort Aqua (budesonide). McNeil Healthcare officially launched prescription strength over-the-counter Rhinocort Aqua (budesonide) nasal spray, marketed as Rhinocort Allergy spray (AstraZeneca, oral communication, 2017).

(Drugs@FDA 2017, Drug Facts and Comparisons 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Beclomethasone	Budesonide (OTC)	Ciclesonide	Flunisolide	Fluticasone furoate	Fluticasone furoate (OTC)	Fluticasone propionate	Fluticasone propionate (OTC)	Mometasone	Triamcinolone	Triamcinolone (OTC)
Indications for Prescription Products											
Treatment/relief of symptoms of SAR and PAR	✔ (age ≥6)*		✔ (age ≥12)†		✔ (age ≥2)						
Treatment of nasal symptoms of SAR	✔ (age ≥4)‡		✔ (age ≥6)§	✔ (age ≥6)					✔ (age ≥2)	✔ (age ≥2)	
Treatment of nasal symptoms of PAR	✔ (age ≥4)‡		✔ (age ≥12)§	✔ (age ≥6)					✔ (age ≥2)	✔ (age ≥2)	
Treatment/relief of nasal congestion associated with SAR									✔ (age ≥2)		
Prophylaxis of nasal symptoms of SAR									✔ (age ≥12)		
Relief of symptoms of nonallergic (vasomotor) rhinitis	✔ (age ≥6)*										
Management of nasal symptoms of perennial nonallergic rhinitis							✔ (age ≥4)				
Treatment of nasal polyps							✔ (age ≥18)#		✔ (age ≥18)		
Prevention of recurrence of nasal polyps following surgical removal	✔ (age ≥6)*										
OTC Uses											

Indication	Beclomethasone	Budesonide (OTC)	Ciclesonide	Flunisolide	Fluticasone furoate	Fluticasone furoate (OTC)	Fluticasone propionate	Fluticasone propionate (OTC)	Mometasone	Triamcinolone	Triamcinolone (OTC)
Temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, and itchy nose		✔ (age ≥6)									✔ (age ≥2)
Temporary relief of symptoms of hay fever or other upper respiratory allergies: nasal congestion, runny nose, sneezing, itchy nose, and itchy, watery eyes						✔ (age ≥2)‖		✔ (age ≥4)			

OTC = over-the-counter
*Beconase AQ
†Zetonna
‡Qnasl
§Omnaris
#Xhance
‖Itchy, watery eyes use is for patients ≥12 years of age

(*Prescribing information: Beconase AQ, 2015; Flonase Allergy Relief, 2017; Flonase Sensimist, 2017; flunisolide, 2016; fluticasone propionate, 2016; Nasacort Allergy 24HR, 2016; Nasonex, 2013; Omnaris, 2013; Qnasl, 2017; Rhinocort Allergy, 2017; triamcinolone, 2013; Xhance, 2017; Zetonna, 2014*)

- 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

- Daily administration of intranasal corticosteroids is associated with statistically significant improvements in allergy-related total nasal symptom score (TNSS) and health related quality of life scores. Numerous head-to-head clinical trials comparing the available intranasal corticosteroids have generally demonstrated no significant clinical differences among the available intranasal corticosteroids with regard to efficacy. Some studies have reported differences in sensory perceptions and patient preference with 1 agent compared to another. Patients administering the agents noted differences in odor, aftertaste, and severity of irritation, though these differences were not associated with differences in efficacy between the agents (Aasand et al, 1982; Al-Mohaimeid, 1993; Andersson et al, 1995; Bachert et al, 2002; Bachert et al, 2004; Berger et al, 2003; Day et al, 1998; Drouin et al 1996; Graft et al, 1996; Gross et al, 2002; Haye et al, 1993; Hebert et al, 1996; Khanna et al, 2005; LaForce et al, 1994; Langrick, 1984; Lumry et al, 2003; Mak et al, 2013; Mandl et al, 1997; McAllen et al, 1980; McArthur, 1994; Meltzer et al, 2005; Meltzer et al, 2008; Meltzer et al, 2010; Naclerio et al, 2003; Ratner et al, 1992; Sahay et al, 1980; Shah et al, 2003; Sipila et al, 1983; Small et al, 1997; Stern et al, 1997; Stokes et al, 2004; Svendsen et al, 1989; Van As et al, 1993; Vanzieleghem et al, 1987; Varshney et al, 2012; Welsh et al, 1987; Winder et al, 1993, Y1zaki et al, 2016).
- Head-to-head trials evaluating the efficacy and safety of beclomethasone, fluticasone propionate and flunisolide demonstrate that these agents are comparable to other agents within the class. However, additional results of these studies reinforce that all of the intranasal corticosteroids should be considered equally efficacious (Aasand et al, 1984; Bachert et al, 2004; Berger et al, 2003; Drouin et al, 1996; Mak et al, 2013; McAllen et al, 1980; Meltzer et al, 2010; Meltzer et al, 2008; Ratner et al, 1992; Sahay et al, 1980; Sipila et al, 1983; Small et al, 1997; Stokes et al, 2004; Van As et al, 1993).
- To date, the newly approved intranasal corticosteroid aerosol formulations have been demonstrated to be significantly more effective compared to placebo. In a 6-week study of patients with PAR, aerosolized beclomethasone significantly improved reflective TNSS compared to placebo (-2.46 vs -1.63; P<0.001). Furthermore, beclomethasone was associated with a statistically significant improvement in quality of life score compared to placebo (P=0.001) (Meltzer et al, 2012). A 2-week study of beclomethasone nasal aerosol 80 µg daily in pediatric patients 6 to 11 years of age with SAR also demonstrated improvement in reflective TNSS compared to placebo (-1.9 vs -1.2; P<0.001) (Storms et al, 2013). A 12-week study of beclomethasone nasal aerosol 80 µg daily in pediatric patients 4 to 11 years of age with perennial allergic rhinitis demonstrated improvement in both reflective and instantaneous TNSS compared to placebo (mean treatment difference -0.53 [P=0.009] and -0.52 [P=0.008], respectively) (Berger et al, 2015).
- The aerosolized ciclesonide formulation has also been shown to significantly improve symptoms of allergic rhinitis compared to placebo. In a study by Ratner et al, ciclesonide administered at a daily dose of 80 µg or 160 µg reduced reflective TNSS by 15.1 and 16%, respectively, compared to 3.7% in the placebo group (P<0.001 for both). In addition, significant improvements were observed with both doses of ciclesonide compared to placebo with regard to ocular symptom scores and quality of life (P<0.001 for both). Similar improvements in outcomes were reported in additional studies of up to 26 weeks duration (Berger et al, 2012; LaForce et al, 2009; Mohar et al, 2012; Ratner et al, 2010; Ratner et al, 2012).
- A systematic review of 40 studies evaluated the use of topical corticosteroids in the treatment or prevention of recurrence of nasal polyps. Topical corticosteroids were effective compared to placebo in the improvement in overall symptoms, nasal obstruction, and a reduction in the size of polyps. Additionally, topical corticosteroids prevented the regrowth of polyps following surgery. No differences in adverse events between topical corticosteroids and placebo were observed (Kalish et al, 2012).
- 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 met inclusion criteria to compare agents of 6 classes for relative efficacy. Agents included oral and nasal antihistamines and decongestants, intranasal corticosteroids, leukotriene modifiers, cromolyn, ipratropium, and normal saline. 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 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. No information

was available about the use of these 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).

- A meta-analysis evaluated nasal corticosteroids, sublingual allergen immunotherapy (SLIT), second generation H1-antihistamines, combination azelastine hydrochloride with fluticasone propionate nasal spray, and montelukast for the treatment of SAR. By indirect comparison, nasal corticosteroids and grass pollen SLIT tablets had a greater relative clinical impact on symptom scores compared to azelastine hydrochloride combined with fluticasone propionate nasal spray, second generation H1-antihistamines, and montelukast (Devillier et al, 2014). In a similar indirect, meta-analysis, SLIT (timothy grass and ragweed) and mometasone furoate improved TNSS to a greater extent than montelukast and desloratadine in the treatment of both SAR and PAR (Durham et al, 2016).
- A meta-analysis compared the effects of intranasal corticosteroids for treatment of chronic rhinosinusitis. A total of 9 randomized controlled trials were included. There was no evidence that 1 intranasal spray was more effective than another for disease severity or disease-specific quality of life. Epistaxis was more common with higher doses compared to lower doses (Chong et al, 2016).

CLINICAL GUIDELINES

- Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe symptoms. Consensus guidelines do not recommend the use of 1 intranasal corticosteroid product over another. Intranasal corticosteroids combined with intranasal antihistamines are considered to be more effective than either alone in the treatment of allergic rhinitis. Addition of oral antihistamines is not effective (Bousquet et al, 2016; Brozek et al, 2017; Dykewicz et al, 2017; Seidman et al, 2015; Wallace et al, 2008).

SAFETY SUMMARY

- The intranasal corticosteroids are contraindicated in patients with hypersensitivity to any of the ingredients.
- Intranasal corticosteroids should not be used in patients with recent nasal septal ulcers, nasal surgery or trauma, as they may impair wound healing. Intranasal corticosteroids should be used cautiously, if at all, in patients with untreated infections.
- Systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur when intranasal steroids are used at higher-than-recommended doses or in susceptible individuals at recommended doses. Patients using corticosteroids may be more susceptible to infection; specific effects of the dose, route and duration of use are not known. Intranasal corticosteroids may cause increased intraocular pressure, blurred vision, glaucoma and/or cataracts. Growth velocity in pediatric patients may be reduced with intranasal corticosteroids.
- However, as a result of both the route of administration and the relatively low systemic bioavailability of these agents, intranasal corticosteroids are generally not associated with any clinically significant systemic adverse events. Moreover, drug interactions are limited when administered at recommended doses. The most common adverse events include nasal irritation and mild epistaxis.

(*Drug Facts and Comparisons 2017*)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
Beclomethasone (Beconase AQ, Qnasl)	Aerosol (Qnasl), Suspension (Beconase AQ)	IN	PAR, SAR: Aerosol: 2 actuations in each nostril once daily Suspension: 1 to 2 sprays in each nostril twice daily	Nasal polyps, nonallergic (vasomotor) rhinitis, PAR, SAR in children 6 to 12 years: Suspension: initial, 1 inhalation in each nostril twice daily; maximum, 2 inhalations in each nostril twice daily	The unit should be primed by releasing 6 sprays (suspension) or 4 sprays (aerosol) before initial use and reprime if not used for 7 days.

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
			Nasal polyps, nonallergic (vasomotor) rhinitis: Suspension: 1 to 2 sprays in each nostril twice daily	PAR, SAR in children 4 to 11 years: Aerosol: 1 actuation (40 µg strength) in each nostril once daily	
Budesonide (Rhinocort Allergy)	OTC suspension	IN	Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily; once symptoms improve, reduce to 1 spray in each nostril once daily	Hay fever or other upper respiratory allergies in children 6 to 12 years: OTC suspension: 1 spray in each nostril once daily; maximum, 2 sprays in each nostril once daily	The unit should be primed by releasing 8 sprays and reprime if not used for 2 days.
Ciclesonide (Omnaris, Zetonna)	Aerosol (Zetonna), suspension (Omnaris)	IN	PAR, SAR: Aerosol: 1 inhalation in each nostril once daily Suspension: 2 sprays in each nostril once daily	SAR in children ≥ 6 years old: Suspension: 2 sprays in each nostril once daily	The unit should be primed by releasing 8 sprays (suspension) or 3 sprays (aerosol) and reprime if not used for 4 days (suspension) or 10 days (aerosol).
Flunisolide	Suspension	IN	PAR, SAR: Suspension: 2 sprays in each nostril twice daily; maximum, 8 sprays in each nostril per day	PAR, SAR in children 6 to 14 years: Suspension: 1 spray in each nostril 3 times daily or 2 sprays in each nostril twice daily; maximum, 4 inhalations in each nostril per day	The unit should be primed before initial use by releasing 5 or 6 sprays and reprime if not used for 5 days or more, or if it has been disassembled for cleaning.
Fluticasone furoate (Flonase Sensimist)	OTC suspension	IN	Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily for 1 week; maintenance, 1 or 2 sprays in each nostril once daily, as needed to treat symptoms	Hay fever or other upper respiratory allergies in children 2 to 11 years: OTC suspension: 1 spray in each nostril once daily	The unit should be primed before initial use, when not used for 30 days or longer, or if the cap has been left off for 5 days or longer, by spraying until a fine mist appears.
Fluticasone propionate (Flonase Allergy Relief, fluticasone, Xhance)	Rx and OTC suspension	IN	Perennial nonallergic rhinitis: Rx suspension: 2 sprays in each nostril once daily or 1 spray in each nostril twice daily; may reduce to 1	Perennial nonallergic rhinitis in children ≥ 4 years old: Rx suspension: 1 spray in each nostril once daily; maximum, 2	The unit should be primed by releasing 6 sprays (Flonase or fluticasone) or 7 sprays (Xhance) until a fine spray appears before initial use and

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
			spray in each nostril once daily for maintenance therapy Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily for 1 week; maintenance, 1 or 2 sprays in each nostril once daily, as needed to treat symptoms Nasal polyps (Xhance): 1 spray in each nostril twice daily; 2 sprays in each nostril twice daily may be effective in some	sprays in each nostril once daily Hay fever or other upper respiratory allergies in children 4 to 11 years: OTC suspension: 1 spray in each nostril once daily	if not used for a week or more.
Mometasone (Nasonex)	Suspension	IN	PAR, SAR: Suspension: 2 sprays in each nostril once daily Nasal polyps in adults ≥18 years old: Suspension: 2 sprays in each nostril once or twice daily	PAR, SAR in children 2 to 11 years: Suspension: 1 spray in each nostril once daily	The unit should be primed before initial use by actuating 10 times or until a fine spray appears. If unused for more than 7 days, it should be re-primed by actuating 2 times or until a fine spray appears.
Triamcinolone (triamcinolone, Nasacort Allergy 24HR)	Rx and OTC suspension	IN	SAR and PAR: Rx suspension: two sprays in each nostril once daily; maintenance, one spray in each nostril once daily. Hay fever or other upper respiratory allergies: OTC suspension: 2 sprays in each nostril once daily; maintenance, 1 inhalation in each nostril once daily	SAR and PAR in children 6 to 12 years old: One spray in each nostril once daily; maximum, two sprays in each nostril once daily SAR and PAR in children 2 to 5 years old: One spray in each nostril once daily Hay fever or other upper respiratory allergies in children 6 to 12 years: OTC Suspension: 1 spray in each nostril	The unit should be primed before initial use (5 sprays for Rx) and if not used for more than 2 weeks by spraying until a fine mist is produced.

Drug	Available Formulations	Route	Usual Recommended Frequency		Comments
			Adults	Pediatric	
				once daily; maximum, 2 sprays in each nostril once daily Hay fever or other upper respiratory allergies in children 2 to under 6 years: OTC Suspension: 1 spray in each nostril once daily	

See the current prescribing information for full details
Abbreviation: IN = intranasal or nasal inhalation, OTC = over the counter, PAR = perennial allergic rhinitis, Rx = prescription, SAR = seasonal allergic rhinitis

CONCLUSION

- Intranasal corticosteroids are used for the management of allergic rhinitis, some forms of nonallergic rhinitis and nasal polyps. They are generally well tolerated and are associated with limited drug interactions due to their localized administration and limited systemic absorption. Like other corticosteroids, intranasal corticosteroids carry warnings regarding use in patients with active infection and the development of signs of adrenal insufficiency, particularly with the administration of higher-than-recommended doses (Wallace et al, 2008).
- Intranasal corticosteroids are considered first-line agents for the treatment of allergic rhinitis, especially for patients with moderate to severe symptoms. Consensus guidelines do not recommend the use of one intranasal corticosteroid product over another (Bousquet et al, 2016; Brozek et al, 2017; Dykewicz et al, 2017; Seidman et al, 2015; Wallace et al, 2008).
- All available intranasal corticosteroids have demonstrated safety and efficacy for their respective indications. These agents have been shown to be effective in reducing rhinitis-related nasal symptoms such as congestion, rhinorrhea, sneezing, nasal itch, and postnasal drip. The differences in tolerability and sensory perceptions noted in clinical trials were minor and did not translate into differences in outcomes. The results of multiple head-to-head trials have generally failed to demonstrate clinically significant differences between products (Aasand et al, 1982; Al-Mohaimeid, 1993; Andersson et al, 1995; Bachert et al, 2004; Bachert et al; 2002; Berger et al, 2003; Day et al, 1998; Drouin et al. 1996; Graft et al, 1996; Gross et al, 2002; Haye et al, 1993; Hebert et al, 1996; LaForce et al, 1994; Langrick, 1984; Lumry et al, 2003; Mak et al, 2013; Mandl et al, 1997; McAllen et al, 1980; McArthur, 1994; Meltzer et al, 2005; Meltzer et al, 2008; Meltzer et al, 2010; Naclerio et al, 2003; Ratner et al, 1992; Sahay et al, 1980; Shah et al, 2003; Sipila et al, 1983; Small et al, 1997; Stern et al, 1997; Stokes et al, 2004; Svendsen et al, 1989; Van As et al, 1993; Vanzieleghem et al, 1987; Varshney et al, 2012; Welsh et al, 1987; Winder et al, 1993).
- Two nasal aerosol formulations, beclomethasone (Qnasl) and ciclesonide (Zetonna), have been approved by the FDA for the relief of symptoms associated with PAR and SAR. The other intranasal corticosteroid products are formulated as aqueous suspensions, which may be bothersome to patients due to the potential of the suspension to drip down or out of the nose following administration.

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