

April 18, 2006

Roger Citron R.Ph.  
Montana Department of  
Public Health and Human Services  
1400 Broadway  
Helena, MT 59620

Dear Mr. Citron:

In response to the Montana Medicaid Drug Use Review Board/Formulary Committee Meeting, we are providing you with a dossier that is consistent with the Academy of Managed Care Pharmacy's (AMCP) format for pharmaceutical manufacturers for your consideration at the Preferred Drug List review beginning in May 3, 2006. Additionally, at your request, we are providing the Nasonex<sup>®</sup> (mometasone furoate monohydrate) Nasal Spray, 50 mcg AMCP Dossier in an electronic format (CD) to facilitate your review process.\*

The purpose of this formulary submission dossier is to present the clinical rationale to support the use of Nasonex<sup>®</sup> for the treatment of the nasal symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and nasal polyps within your health plan. This dossier presents the ways in which Nasonex<sup>®</sup> provides value in the management of SAR, PAR, and nasal polyps.

### **Structure of This Dossier**

**Section 1** provides product information for Nasonex<sup>®</sup>, including its description and place in therapy.

**Section 2** provides a summary of the supporting clinical evidence for Nasonex<sup>®</sup>, based on results from safety efficacy studies.

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\*This information is provided as a professional service in response to your unsolicited inquiry. It is intended to provide you with a fair, balanced, and objective review of the available scientific literature and/or data that you requested. This response is not intended to offer recommendations for use of this or any product inconsistent with approved product labeling. Please refer to the package insert for full prescribing information.

**Section 3** provides a discussion of the overall product value of Nasonex<sup>®</sup>.

**Section 4** provides the supporting information (references and checklist) to this dossier.

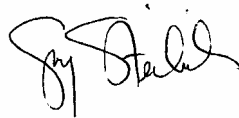
Should you have any questions on the clinical portion of the dossier, please contact Global Drug Information Services at (800) 526-4099.

The following person may be contacted to provide additional information regarding submission materials:

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Based on the findings, Schering believes Nasonex<sup>®</sup> should be placed on the preferred drug list of contract drugs without restrictions.

Sincerely,



Gay Steinbrick, Pharm.D.  
Sr. Director, Global Drug Information Services

2006-19511

Enclosures:

CD of Nasonex<sup>®</sup> AMCP Dossier  
Nasonex<sup>®</sup> Product Information sheet  
References  
Formulary Submission Checklist

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# 1. PRODUCT INFORMATION

## 1.1 PRODUCT DESCRIPTION

Nasonex Nasal Spray, 50 mcg is a metered-dose, manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate calculated on the anhydrous basis; in an aqueous medium containing glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80.

### a) Product Overview: Generic, Brand Name and Therapeutic Class of Product:

**Generic name:** mometasone furoate monohydrate Nasal Spray, 50 mcg

**Brand name:** Nasonex

**Therapeutic class of the product:** Intranasal corticosteroid

### b) Dosage Form, Including Strengths and Package Size:

Nasonex is a nasal spray supplied in a white, high-density, polyethylene bottle fitted with a white metered-dose, manual spray pump, and blue cap. It contains 17 g of product formulation, 120 sprays, each delivering 50 mcg of mometasone furoate per actuation.

### c) The National Drug Code (NDC):

00085-1288-01

### d) A Copy of the Official Product Labeling/Literature :

Enclosed

### e) The AWP and WAC\* Cost Per Unit Size:

Schering-Plough does not declare an AWP. WAC\* per unit size is \$67.77.

### f) AHFS or other Drug Classification:

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\* The price shown is Schering-Plough's list price for its wholesale customers. It does not reflect prompt pay discount. In addition, it does not reflect prices, rebates or discounts that may be extended to Managed Care and other buying organizations.

52:08 Eye, Ear Nose, and Throat Preparations: Anti-inflammatory Agent

## **g) FDA Approved Indications and Other Studied Uses:**

### **FDA Approved Indications:**

Nasonex Nasal Spray, 50 mcg is indicated for the treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis, in adults and pediatric patients 2 years of age and older. Nasonex Nasal Spray, 50 mcg is indicated for the prophylaxis of the nasal symptoms of seasonal allergic rhinitis in adult and adolescent patients 12 years and older. In patients with a known seasonal allergen that precipitates nasal symptoms of seasonal allergic rhinitis, initiation of prophylaxis with Nasonex Nasal Spray, 50 mcg is recommended 2 to 4 weeks prior to the anticipated start of the pollen season. Safety and effectiveness of Nasonex Nasal Spray, 50 mcg in pediatric patients less than 2 years of age have not been established. Nasonex Nasal Spray, 50 mcg, is indicated for the treatment of nasal polyps in patients 18 years of age and older. Safety and effectiveness of Nasonex Nasal Spray, 50 mcg, for the treatment of nasal polyps in pediatric patients less than 18 years of age have not been established.

### **Other Studied Uses (Not FDA Approved):**

#### **Rhinosinusitis:**

Several trials have examined the efficacy and safety of Nasonex Nasal Spray for the treatment of rhinosinusitis. The FDA reviewed adjunctive treatment in acute sinusitis and Nasonex was not approved for this use. Please refer to Section 2 for supporting clinical information.

#### **Perennial Non-Allergic Rhinitis (PNAR):**

One trial has examined the efficacy and safety of Nasonex Nasal Spray for the treatment of PNAR. Please refer to Section 2 for supporting clinical information.

#### **Cough associated with SAR:**

One trial has examined the efficacy and safety of Nasonex Nasal Spray for the treatment of cough associated with SAR. Please refer to Section 2 for supporting clinical information.

## **h) Pharmacology:**

Nasonex Nasal Spray, 50 mcg is a corticosteroid demonstrating anti-inflammatory properties. The precise mechanism of corticosteroid action on allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of effects on multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

In two clinical studies utilizing nasal antigen challenge, Nasonex Nasal Spray, 50 mcg decreased some markers of the early- and late-phase allergic response. These observations included decreases (vs placebo) in histamine and eosinophil cationic protein levels, and reductions (vs baseline) in eosinophils, neutrophils, and epithelial cell adhesion proteins. The clinical significance of these findings is not known.

The effect of Nasonex Nasal Spray, 50 mcg on nasal mucosa following 12 months of treatment was examined in 46 patients with allergic rhinitis. There was no evidence of atrophy and there was a marked reduction in intraepithelial eosinophilia and inflammatory cell infiltration (eg, eosinophils, lymphocytes, monocytes, neutrophils, and plasma cells).

**i) Pharmacokinetics/Pharmacodynamics:**

**Absorption:** Mometasone furoate monohydrate administered as a nasal spray is virtually undetectable in plasma from adult and pediatric subjects despite the use of a sensitive assay with a lower quantitation limit (LOQ) of 50 pcg/mL.

**Distribution:** The *in vitro* protein binding for mometasone furoate was reported to be 98% to 99% in concentration range of 5 to 500 ng/mL.

**Metabolism:** Studies have shown that any portion of a mometasone furoate dose which is swallowed and absorbed undergoes extensive metabolism to multiple metabolites. There are no major metabolites detectable in plasma. Upon *in vitro* incubation, one of the minor metabolites formed is 6 $\beta$ -hydroxy-mometasone furoate. In human liver microsomes, the formation of the metabolite is regulated by cytochrome P-450 3A4 (CYP3A4).

**Elimination:** Following intravenous administration, the effective plasma elimination half-life of mometasone furoate is 5.8 hours. Any absorbed drug is excreted as metabolites mostly via the bile, and to a limited extent, into the urine.

**Pharmacodynamics:**

Four clinical pharmacology studies have been conducted in humans to assess the effect of Nasonex Nasal Spray, 50 mcg at various doses on adrenal function. In one study, daily doses of 200 and 400 mcg of Nasonex Nasal Spray, 50 mcg and 10 mg of prednisone were compared to placebo in 64 patients with allergic rhinitis. Adrenal function before and after 36 consecutive days of treatment was assessed by measuring plasma cortisol levels following a 6-hour Cortrosyn (ACTH) infusion and by measuring 24-hour urinary-free cortisol levels. Nasonex Nasal Spray, 50 mcg, at both the 200- and 400-mcg dose, was not associated with a statistically significant decrease in mean plasma cortisol levels post-Cortrosyn infusion or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo. A statistically significant decrease in the mean plasma cortisol levels post-Cortrosyn infusion and 24-hour urinary-free cortisol levels was detected in the prednisone treatment group compared to placebo.

A second study assessed adrenal response to Nasonex Nasal Spray, 50 mcg (400 and 1600 mcg/day), prednisone (10 mg/day), and placebo, administered for 29 days in 48 male volunteers. The 24-hour plasma cortisol area under the curve ( $AUC_{0-24}$ ), during and after an 8-hour Cortrosyn infusion and 24-hour urinary-free cortisol levels were determined at baseline and after 29 days of treatment. No statistically significant differences of adrenal function were observed with Nasonex Nasal Spray, 50 mcg compared to placebo.

A third study evaluated single, rising doses of Nasonex Nasal Spray, 50 mcg (1000, 2000, and 4000 mcg/day), orally administered mometasone furoate (2000, 4000, and 8000 mcg/day), orally administered dexamethasone (200, 400, and 800 mcg/day), and placebo (administered at the end of each series of doses) in 24 male volunteers. Dose administrations were separated by at least 72 hours. Determination of serial plasma cortisol levels at 8 AM and for the 24-hour period following each treatment were used to calculate the plasma cortisol area under the curve ( $AUC_{0-24}$ ). In addition, 24-hour urinary-free cortisol levels were collected prior to initial treatment administration and during the period immediately following each dose. No statistically significant decreases in the plasma cortisol AUC, 8 AM cortisol levels, or 24-hour urinary-free cortisol levels were observed in volunteers treated with either Nasonex Nasal Spray, 50 mcg or oral mometasone, as compared with placebo treatment. Conversely, nearly all volunteers treated with the three doses of dexamethasone demonstrated abnormal 8 AM cortisol levels (defined as a cortisol level  $< 10$  mcg/dL), reduced 24-hour plasma AUC values, and decreased 24-hour urinary-free cortisol levels, as compared to placebo treatment.

In a fourth study, adrenal function was assessed in 213 patients with nasal polyps before and after 4 months of treatment with either Nasonex Nasal Spray, 50 mcg, (200 mcg once or twice daily) or placebo by measuring 24-hour urinary-free cortisol levels. Nasonex Nasal Spray, 50 mcg, at both doses (200 and 400 mcg/day), was not associated with statistically significant decreases in the 24-hour urinary-free cortisol levels compared to placebo.

Three clinical pharmacology studies have been conducted in pediatric patients to assess the effect of mometasone furoate nasal spray on the adrenal function at daily doses of 50, 100, and 200 mcg vs placebo. In one study, adrenal function before and after 7 consecutive days of treatment was assessed in 48 pediatric patients with allergic rhinitis (ages 6 to 11 years) by measuring morning plasma cortisol and 24-hour urinary-free cortisol levels. Mometasone furoate nasal spray, at all three doses, was not associated with a statistically significant decrease in mean plasma cortisol levels or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo. In the second study, adrenal function before and after 14 consecutive days of treatment was assessed in 48 pediatric patients (ages 3 to 5 years) with allergic rhinitis by measuring plasma cortisol levels following a 30-minute Cortrosyn infusion. Mometasone furoate nasal spray, 50 mcg, at all three doses (50, 100, and 200 mcg/day), was not associated with a statistically significant decrease in mean plasma cortisol levels post-Cortrosyn infusion compared to placebo.

All patients had a normal response to Cortrosyn. In the third study, adrenal function before and after up to 42 consecutive days of once-daily treatment was assessed in 52 patients with allergic rhinitis (ages 2 to 5 years), 28 of whom received mometasone furoate nasal spray, 50 mcg per nostril (total daily dose 100 mcg), by measuring morning plasma cortisol and 24-hour urinary-free cortisol levels. Mometasone furoate nasal spray was not associated with a statistically significant decrease in mean plasma cortisol levels or a statistically significant decrease in the 24-hour urinary-free cortisol levels compared to placebo.

**j) Contraindications :**

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

**k) Warnings/Precautions :**

**Warnings:** The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal; ie, joint and/or muscular pain, lassitude, and depression. Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to topical corticosteroids, with careful monitoring for acute adrenal insufficiency in response to stress. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroid dosing may cause a severe exacerbation of their symptoms.

If recommended doses of intranasal corticosteroids are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneiform lesions, and cushingoid features. If such changes occur, topical corticosteroids should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

**Precautions: General:** Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use section). In clinical studies with Nasonex Nasal Spray, 50 mcg, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, use of Nasonex Nasal Spray, 50 mcg should be discontinued and appropriate local or systemic therapy instituted, if needed.

Nasal corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infection of the respiratory tract, or in untreated fungal, bacterial, systemic viral infections, or ocular herpes simplex.

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of mometasone furoate monohydrate. Extremely rare instances of wheezing have been reported.

Rare instances of nasal septum perforation and increased intraocular pressure have also been reported following the intranasal application of aerosolized corticosteroids. As with any long-term topical treatment of the nasal cavity, patients using Nasonex Nasal Spray, 50 mcg over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septum ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Glaucoma and cataract formation was evaluated in one controlled study of 12 weeks' duration and one uncontrolled study of 12 months' duration in patients treated with Nasonex Nasal Spray, 50 mcg at 200 mcg/day, using intraocular pressure measurements and slit lamp examination. No significant change from baseline was noted in the mean intraocular pressure measurements for the 141 Nasonex-treated patients in the 12-week study, as compared with 141 placebo-treated patients. No individual Nasonex-treated patient was noted to have developed a significant elevation in intraocular pressure or cataracts in this 12-week study. Likewise, no significant change from baseline was noted in the mean intraocular pressure measurements for the 139 Nasonex-treated patients in the 12-month study and again, no cataracts were detected in these patients. Nonetheless, nasal and inhaled corticosteroids have been associated with the development of glaucoma and/or cataracts. Therefore, close follow-up is warranted in patients with a change in vision and with a history of glaucoma and/or cataracts.

When nasal corticosteroids are used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, Nasonex Nasal Spray, 50 mcg should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

**I) Adverse Effects:**

**Allergic Rhinitis.** In controlled US and international clinical studies, a total of 3210 adult and adolescent patients ages 12 years and older with allergic rhinitis received treatment with Nasonex Nasal Spray, 50 mcg at doses of 50 to 800 mcg/day. The majority of patients (n = 2103) were treated with 200 mcg/day. In controlled US and international studies, a total of 990 pediatric patients (ages 3 to 11 years) with allergic rhinitis received treatment with Nasonex Nasal Spray, 50 mcg, at doses of 25 to 200 mcg/day. The majority of pediatric patients (720) were treated with 100 mcg/day. A total of 513 adult, adolescent, and pediatric patients have been treated for 1 year or longer. The overall incidence of adverse events for patients treated with Nasonex Nasal Spray, 50 mcg was comparable to patients treated with the vehicle placebo. Also, adverse events did not differ significantly based on age, sex, or race. Three percent or less of patients in clinical trials discontinued treatment because of adverse events; this rate was similar for the vehicle and active comparators.

All adverse events (regardless of relationship to treatment) reported by 5% or more of adult and adolescent patients ages 12 years and older who received Nasonex Nasal Spray, 50 mcg, 200 mcg/day and by pediatric patients ages 3 to 11 years who received Nasonex Nasal Spray, 50 mcg, 100 mcg/day in clinical trials vs placebo and that were more common with Nasonex Nasal Spray, 50 mcg than placebo, are displayed in the table below.

**Adverse Events From Controlled Clinical Trials In Seasonal Allergic and Perennial Allergic Rhinitis (Percent Of Patients Reporting)**

	Adult and Adolescent Patients 12 years and older		Pediatric Patients Ages 3 to 11 years	
	Nasonex 200 mcg (n = 2103)	Vehicle placebo (n = 1671)	Nasonex 100 mcg (n = 374)	Vehicle placebo (n = 376)
Headache	26	22	17	18
Viral Infection	14	11	8	9
Pharyngitis	12	10	10	10
Epistaxis/Blood Tinged Mucus	11	6	8	9
Coughing	7	6	13	15
Upper Respiratory Tract Infection	6	2	5	4
Dysmenorrhea	5	3	1	0
Musculoskeletal Pain	5	3	1	1
Sinusitis	5	3	4	4
Vomiting	1	1	5	4

Other adverse events which occurred in less than 5% but greater than or equal to 2% of mometasone furoate adult and adolescent patients (ages 12 years and older) treated with 200 mcg doses (regardless of relationship to treatment), and more frequently than in the placebo group included: arthralgia, asthma, bronchitis, chest pain, conjunctivitis, diarrhea, dyspepsia, earache, flu-like symptoms, myalgia, nausea, and rhinitis.

Other adverse events which occurred in less than 5% but greater than or equal to 2% of mometasone furoate pediatric patients ages 3 to 11 years treated with 100-mcg doses vs placebo (regardless of relationship to treatment) and more frequently than in the placebo group included: diarrhea, nasal irritation, otitis media, and wheezing.

The adverse event (regardless of relationship to treatment) reported by 5% of pediatric patients ages 2 to 5 years who received Nasonex Nasal Spray, 50 mcg, 100 mcg/day in a clinical trial vs placebo including 56 subjects (28 each Nasonex Nasal Spray, 50 mcg and placebo) and that was more common with Nasonex Nasal Spray, 50 mcg than placebo, included: upper respiratory tract infection (7% vs 0%, respectively). The other adverse event which occurred in less than 5% but greater than or equal to 2% of mometasone furoate pediatric patients ages 2 to 5 years treated with 100 mcg doses vs placebo (regardless of relationship to treatment) and more frequently than in the placebo group included: skin trauma.

***Nasal Polyps.*** In controlled clinical studies, the types of adverse events observed in patients with nasal polyps were similar to those observed for patients with allergic rhinitis. A total of 594 adult patients (ages 18 to 86 years) received Nasonex Nasal Spray, 50 mcg, at doses of 200 mcg once or twice daily for up to 4 months for treatment of nasal polyps. The overall incidence of adverse events for patients treated with Nasonex Nasal Spray, 50 mcg was comparable to patients treated with the placebo except for epistaxis, which was 9% for 200 mcg once daily, 13% for 200 mcg twice daily, and 5% for placebo.

Rare cases of nasal ulcers and nasal and oral candidiasis were also reported in patients treated with Nasonex Nasal Spray, 50 mcg, primarily in patients treated for longer than 4 weeks.

In postmarketing surveillance of this product, cases of nasal burning and irritation, anaphylaxis and angioedema, and rare cases of nasal septal perforation have been reported. Disturbances of taste and smell have been reported very rarely.

**m) Interactions :**

No significant interactions reported in literature or product labeling.

**n) Dosing and Administration:**

**Allergic Rhinitis: Adults and Children 12 Years of Age and Older:** The recommended dose for prophylaxis and treatment of the nasal symptoms of seasonal allergic rhinitis and treatment of the nasal symptoms of perennial allergic rhinitis is two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg). In patients with a known seasonal allergen that precipitates nasal symptoms of seasonal allergic rhinitis, prophylaxis with Nasonex Nasal Spray, 50 mcg (200 mcg/day) is recommended 2 to 4 weeks prior to the anticipated start of the pollen season.

**Children 2 to 11 Years of Age:** The recommended dose for treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis is one spray (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 100 mcg).

Improvement in nasal symptoms of allergic rhinitis has been shown to occur within 11 hours after the first dose based on one single-dose, parallel-group study of patients in an outdoor “park” setting (park study) and one environmental exposure unit (EEU) study and within 2 days after the first dose in two randomized, double-blind, placebo-controlled, parallel-group seasonal allergic rhinitis studies. Maximum benefit is usually achieved within 1 to 2 weeks. Patients should use Nasonex Nasal Spray, 50 mcg only once daily for allergic rhinitis at a regular interval.

**Nasal Polyps: Adults 18 years of Age and Older:** The recommended dose for nasal polyps is two sprays (50 mcg of mometasone furoate in each spray) in each nostril twice daily (total daily dose of 400 mcg). A dose of two sprays (50 mcg of mometasone furoate in each spray) in each nostril once daily (total daily dose of 200 mcg) is also effective in some patients.

**o) Access, e.g., Restrictions on Distribution, Supply, Limitations, Anticipated Shortages:**

None anticipated.

**p) Commonly Co-Prescribed / Concomitant Therapies, Including Dosages:**

**Oral Non-sedating Antihistamines:**

Clarinet<sup>®</sup> (desloratadine)<sup>2</sup>: Adults and children 12 years of age and older: Clarinet Tablets-5mg or Clarinet RediTabs Tablets- 5 mg once daily and Clarinet Syrup- 2 teaspoonfuls (5 mg in 10 mL) once daily.

Children 6 to 11 years of age: Clarinet Syrup- 1 teaspoonful (2.5 mg in 5 mL) once daily

Children 12 months to 5 years of age: Clarinet Syrup- ½ teaspoonful (1.25 mg in 2.5 mL) once daily

Children 6 to 11 months of age: Clarinet Syrup- 2 mL (1.0 mg) once daily

Allegra<sup>®</sup> (fexofenadine hydrochloride)<sup>3</sup>: 60 mg twice daily or 180 mg once daily in adults and children 12 years of age and older, 30 mg twice daily in children ages 6 to 11 years of age.

**Oral sedating Antihistamines:**

Zyrtec<sup>®</sup> (cetirizine hydrochloride)<sup>4</sup>: Adults and children 12 years and older: Zyrtec<sup>®</sup> Tablets 5-10 mg daily.

Children 6 to 11 years: Zyrtec<sup>®</sup> Tablets 5-10 mg once daily.

Children 2 to 5 years: Zyrtec Syrup ½ teaspoonful (2.5 mg in 2.5 mL). The dosage may be increased to a maximum of 5 mg per day given as 1 teaspoon syrup once a day or ½ teaspoon syrup given every 12 hours, or one 5 mg chewable tablet once a day.

Children 6 months to 23 months: Zyrtec Syrup ½ teaspoon (2.5 mg in 2.5 mL) once daily. The dose in children 12-23 months of age can be increased to a maximum dose of 5 mg per day.

**Nasal Antihistamines:**

Astelin<sup>®</sup> (azelastine hydrochloride)<sup>5</sup>: In seasonal allergic rhinitis the recommended dose is 2 sprays per nostril twice daily in adults and children 12 years and older and 1 spray per nostril twice daily in children 5 years to 11 years of age.

**Leukotriene Modifiers:**

Singulair<sup>®</sup> (montelukast sodium)<sup>6</sup>: Adults and adolescents 15 years of age and older: Singulair Tablets 10 mg once daily.

Pediatric patients 6 to 14 years of age: Singulair Chewable Tablets- 5 mg once daily.

Pediatric patients 2 to 5 years of age: Singulair Chewable Tables- 4 mg once daily.

Pediatric patients 6 to 23 months of age with perennial allergic rhinitis: Singulair Oral Granules 4- mg once daily.

**Comparison with the pharmacokinetic / pharmacologic profile of other agents in the therapeutic area.  
 Across-label comparisons – Information as reported in the product labeling – Not obtained from comparative trials**

<b>Agent</b>	<b>Onset</b>	<b>Bioavailability</b>	<b>Half-Life</b>	<b>Protein Binding</b>	<b>HPA-axis suppression</b>	<b>Drug Interactions</b>	<b>Indications</b>
<b>Nasonex<sup>®7</sup></b>	11 hours	≤ 0.1%	5.8 hours	98-99%	No statistically significant decrease in plasma cortisol AUC at doses up to 4000 mcg/day (20 times the recommended dose)	No significant interactions reported in literature or product labeling	Treatment of SAR in patients ≥ 2 years of age Treatment of PAR in patients ≥ 2 years of age Prophylaxis of SAR in patients ≥ 12 years of age Treatment of nasal polyps in patients ≥ 18 years of age
<b>Flonase<sup>®8</sup></b>	12 hours	< 2%	7.8 hours	91%	No effect at recommended doses	Coadministration of ritonavir is not recommended. Coadministration of ketoconazole increased plasma concentration of fluticasone propionate and reduced plasma cortisol AUC. Caution should be exercised when coadministered with other potent cytochrome P450 3A4 inhibitors	Treatment of SAR in patients ≥ 4 years of age Treatment of PAR in patients ≥ 4 years of age Treatment of PNAR in patients ≥ 4 years of age
<b>Rhinocort Aqua<sup>®9</sup></b>	10 hours	34%	2-3 hours	85-90%	Small but statistically significant decrease in area under the plasma cortisol-time curve over 24 hours at 256 mcg/day; decrease in 24-hour urinary cortisol (dose-dependent 100-800 mcg/day)	Coadministration of ketoconazole increases plasma concentrations of oral budesonide by more than 7-fold. Coadministration of other known CYP3A4 inhibitors (itraconazole, clarithromycin, erythromycin, etc) may inhibit metabolism and increase systemic exposure to budesonide. Coadministration of cimetidine increased oral bioavailability of budesonide.	Treatment of SAR in patients ≥ 6 years of age Treatment of PAR in patients ≥ 6 years of age

Note: This information is based upon the products' respective Prescribing Information. It is not based upon head-to-head clinical studies

<b>Agent</b>	<b>Onset</b>	<b>Bioavail- ability</b>	<b>Half- Life</b>	<b>Protein Binding</b>	<b>HPA-axis suppression</b>	<b>Drug Interactions</b>	<b>Indications</b>
<b>Nasacort® AQ<sup>10</sup></b>	Within the first day	Not reported in product labeling	3.1 hours	Not reported in product labeling	No statistically significant effect at doses of 220-440 mcg/day	No interactions noted in product labeling	Treatment of SAR in patients ≥ 6 years of age Treatment of PAR in patients ≥ 6 years of age
<b>Beconase AQ<sup>11</sup></b>	Within 3 days	44%	0.5 hour	87%	Dose-dependent with suppression of plasma cortisol concentration at doses of 1600-2000 mcg/day	No interactions noted in product labeling	Treatment of SAR in patients ≥ 6 years of age Treatment of PAR in patients ≥ 6 years of age Treatment of PNAR in patients ≥ 6 years of age Prevention of recurrence of nasal polyps following surgical removal
<b>Nasarel<sup>12</sup></b>	Not reported in product labeling	50%	1-2 hours	Not reported in product labeling	No consistent effect on endogenous cortisol production at average dose of 350-2200 mcg/day	No interactions noted in product labeling	Treatment of SAR in patients ≥ 6 years of age Treatment of PAR in patients ≥ 6 years of age

Note: This information is based upon the products' respective Prescribing Information. It is not based upon head-to-head clinical studies

## 1.2 PLACE OF THE PRODUCT IN THERAPY

### Epidemiology/Risk Factors

Allergic rhinitis (AR) is a common disorder that has traditionally been divided into two conditions, seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Prevalence estimates for AR range from 22.4 million<sup>13</sup> to 39 million<sup>14</sup> or 79.5 million<sup>15</sup> Americans, depending on the definition of the disease. It is estimated that 9.3% to 30% of adults and up to 40% of children suffer from AR. Forty two percent of children are predicted to have developed physician diagnosed AR by the age of six<sup>16</sup>, although the symptoms may be reduced with age.<sup>17</sup> The principal risk factors for AR are the presence of an offending allergen (e.g., pollen, dust mites, pet dander)<sup>18</sup> and a family history of allergy.<sup>19</sup>

Rhinitis occurs in over 75% of patients with allergic asthma and in over 80% of patients with non-allergic asthma.<sup>20</sup> Rhinitis also may be associated with other chronic allergic and airways diseases such as sinusitis, nasal polyposis, and otitis media.<sup>21, 22</sup> It is important to note that in addition to diseases that are primarily respiratory in nature, there may be other associated comorbidities.<sup>23</sup>

This epidemiological data supports the consideration of allergy as a systemic disease with broad manifestations, and supporting more aggressive treatment of allergy to prevent and/or treat comorbid conditions.<sup>23</sup>

Approximately 2% to 4% of the worldwide population suffer from nasal polyps.<sup>24, 25</sup> Nasal polyps are found in 36% of patients with aspirin intolerance, 7% of those with asthma, 0.1% in children, and about 20% in those with cystic fibrosis. Other conditions associated with nasal polyps are Churg-Strauss Syndrome, allergic fungal sinusitis, and cilia dyskinesic syndrome, (Kartagener's) and Young Syndrome. Nasal polyps are statistically more common in nonallergic asthma versus allergic asthma (13% vs 5%,  $p < 0.01$ ). About 40% of patients with surgical polypectomies have recurrences. There appears to be a hereditary factor for developing nasal polyps.<sup>26</sup>

### Pathophysiology

Allergy is defined as an altered state of immune reactivity, usually denoting hypersensitivity, and involves humoral mediators, complement proteins, and the immunoglobulins. One of the most common pathologic features of allergic conditions is the presence of inflammation caused by activation of the immune system.

The allergic response manifesting as allergic rhinitis has three phases: 1) sensitization, representing initial exposure to an allergen, 2) early phase (acute) reaction that occurs within minutes of re-exposure to an allergen, and 3) late phase (chronic) reaction that occurs within hours of re-exposure. Nasonex is shown to affect the early phase response through the reduction of histamine levels,<sup>27</sup> and to attenuate the late phase response through reductions in mediators such as IL-6, IL-8, neutrophils, and eosinophils.<sup>27, 28</sup>

Nasal polyps are characterized as an eosinophil-dominated inflammation of unknown cause. Nasal polyps are benign growths of the mucosa characterized by proliferation of the epithelial layer, glandular hyperplasia, thickening of the basement membrane and edema, focal fibrosis, and cellular infiltration of the stromal layer. The mechanisms leading to these pathologic changes are unclear. Eosinophils are the prominent infiltrating cell. Eosinophils produce a variety of inflammatory mediators and eosinophils infiltrating into the polyps express growth factors, which are relevant to the structural changes seen. Supernatants from nasal polyps were more potent in inducing eosinophil survival than those from healthy normal mucosa.<sup>24, 25, 29, 30</sup>

Interleukin-5 (IL-5) is one of the key-factors for the survival of eosinophils and IL-5 secretion is suppressed by mometasone. Thus, it seems likely that Nasonex would be not only a symptomatic but also an active anti-inflammatory drug for the treatment of nasal polyps.<sup>24, 25, 29, 30</sup>

## **Clinical Presentation**

AR is characterized by nasal congestion, rhinorrhea, sneezing, nasal itching, and postnasal drip. It is also often associated with ocular symptoms.<sup>31</sup> Approximately 40% to 65% of patients with allergic rhinitis will experience congestion.<sup>32</sup> Affected patients often experience fatigue, headache and poor concentration<sup>33</sup> as well as decrements in cognitive performance.<sup>34-36</sup>

The comorbid conditions which may be associated with AR include asthma, rhinosinusitis, otitis media and allergic conjunctivitis.<sup>37</sup> Co-morbidities are significant because they may add to the burden on the patient's health and quality of life.

## **Approaches to treatment – principle options/practice patterns**

The four general principles of managing allergy, as outlined in the Allergy Report<sup>37</sup> are environmental control (i.e. avoidance of allergens), pharmacological therapy, allergen immunotherapy and patient education. Oral antihistamines have historically been the mainstay of pharmacotherapy for allergic rhinitis, and are recommended for patients with persistent mild-to-moderate disease.<sup>37-39</sup> Oral decongestants are also used in patients with congestion, although they are not appropriate for some patients due to side effects and are recommended for short term use only.

Patients with moderate symptoms are generally advised to use intranasal corticosteroids, with or without the supplemental use of oral antihistamines.<sup>37</sup> The ability of intranasal steroids to reduce nasal inflammation, and their relatively favorable side-effect profile has increased their role in the treatment of allergic rhinitis.<sup>40</sup> Studies have also shown that the ability of intranasal steroids to reduce nasal congestion is superior to antihistamines.<sup>41</sup> Intranasal corticosteroids, such as Nasonex, are recommended as first line of therapy when obstruction is a major component of the patient's rhinitis.<sup>37</sup> Additionally, the National Asthma Education and Prevention Program recommends intranasal corticosteroids for the treatment of chronic rhinitis in patients with persistent asthma.<sup>37</sup>

In addition, there are several over-the-counter preparations available for the treatment of the symptoms of rhinitis. Currently, these include first- and second-generation antihistamines, topical decongestants, and oral antihistamine/decongestant combinations. The complexity of proper diagnosis and treatment of allergic diseases, as well as the associated comorbid conditions discussed above, suggest that self-care and self-treatment by patients may often be inappropriate for the long-term treatment of allergic rhinitis.

If pharmacological treatments prove ineffective, patients are recommended to see a specialist and receive immunotherapy when appropriate.<sup>37</sup> It is estimated that immunotherapy is ultimately successful in up to 90% of patients with SAR, and in 70-80% with PAR.<sup>42</sup> However, immunotherapy is generally reserved for patients where there is clear evidence of the relationship between symptoms and an unavoidable allergen and there is difficulty in controlling allergy with pharmacologic management.<sup>37</sup> Other factors such as cost and numerous office visits should also be carefully considered prior to the initiation of immunotherapy.

Based on the available options for treatment of AR, Nasonex presents itself as a solid therapy option due to the patient population. Nasonex is the only nasally inhaled steroid approved for the treatment and prophylaxis of seasonal allergic rhinitis as well as the treatment of perennial allergic rhinitis. Nasonex is also the only nasally inhaled steroid approved for use in children as young as 2 years of age.

Nasonex exhibits strong anti-inflammatory activity *in vitro* and *in vivo*<sup>43-45</sup> and affords clinically significant symptom relief in 28% of patients within 12 hours of the first dose.<sup>46</sup> Nasonex relieves all nasal allergy symptoms, all season long, including congestion, nasal itch, discharge, and sneezing.

Nasonex is well tolerated with a well documented adverse event profile. After one year of therapy no evidence of nasal atrophy and no decrease in percentage of ciliated epithelium was detected. In adults and pediatric patients, clinical trials confirmed that there is no detectable HPA axis suppression and no growth suppression in children ages 3 to 9 years of age.<sup>47</sup>

Intranasal corticosteroids are effective in the relief of symptoms associated with nasal polyps (ie, increased nasal flow and reduction of nasal blockage, sneezing and rhinorrhea) and there is increasing support by the medical community to use nasal steroids as a first line treatment of nasal polyps to avoid the need for surgery. The goals of treatment for nasal polyps are to reduce the size of polyps, reduce the signs and symptoms of the associated rhinitis, improve nasal breathing, restore the sense of smell, and reduce the incidence of recurrence after successful medical or surgical treatment. Nasonex demonstrated a decrease in the recurrence of polyps in nearly half of the subjects treated during clinical trials.<sup>29, 30</sup> Nasonex is the only nasally inhaled steroid approved for use in the treatment of nasal polyps in patients 18 years of age and older. It has been proven to reduce polyp grade and nasal congestion. Nasonex is not indicated to reduce the need for surgery nor to decrease recurrence of polyps following surgery. Please refer to page 25: Section: 2 d. Efficacy in the Treatment of Nasal Polyps.

## 2. SUPPORTING CLINICAL INFORMATION

### 2.1 SUMMARIZING KEY CLINICAL STUDIES

The clinical support information for Nasonex Nasal Spray is organized as follows:

- A. Efficacy in the Treatment of PAR
  - Comparison to beclomethasone dipropionate
  - Comparison to fluticasone propionate
- B. Efficacy in the Treatment of SAR
  - Comparison to beclomethasone dipropionate
- C. Efficacy in the Prophylaxis of SAR
  - Comparison to beclomethasone dipropionate
  - Comparison to budesonide
- D. Efficacy in the Treatment of Nasal Polyps
- E. Onset of Action
- F. Safety
- G. Pediatric Data
- H. Efficacy in Nasal Congestion Associated with Allergic Rhinitis
- I. Off-Label Use
  - Sinusitis and rhinosinusitis
  - Perennial non-allergic rhinitis (PNAR)
  - Cough associated with SAR

#### a) Efficacy in the Treatment of Perennial Allergic Rhinitis

##### *Comparison to beclomethasone dipropionate*

Several studies evaluated the use of Nasonex Nasal Spray in the treatment of perennial allergic rhinitis (PAR). The primary efficacy variable for each of these studies was the average change from baseline in total morning (AM) plus evening (PM) diary nasal symptom scores over the first 15 days of treatment. **Drouin et al.**<sup>48</sup> conducted a 12-week, randomized, double-blind, double-dummy, placebo-controlled study to compare mometasone 200 mcg once daily (QD), beclomethasone 200 mcg\* twice daily, and placebo in 427 patients with moderate to severe PAR.

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\* Recommended dosage for beclomethasone dipropionate is 168 to 336 mcg/day in two divided doses for patients  $\geq$  12 years old.

During the first 15 days, the patient-rated total nasal symptom scores were significantly reduced ( $p \leq 0.01$ ) from baseline in both active treatment groups, and this effectiveness was maintained throughout the study. Both mometasone and beclomethasone showed a significant reduction ( $p \leq 0.01$ ) in symptom severity at all time points when compared with placebo. Mometasone and beclomethasone were not statistically different from each other at any time point.

Results of secondary efficacy variables, physician's evaluation and patient's response to treatment, were similar to results of symptoms evaluations. Patients treated with either mometasone or beclomethasone showed a more favorable response to treatment than those treated with placebo. While numerical superiority to placebo for both active treatments was evident at each time period, statistical superiority was not always achieved. Mometasone was statistically superior to placebo on days 8, 15, and week 12 ( $p \leq 0.01$ ); beclomethasone was superior to placebo on days 8, 15, and 29 ( $p \leq 0.01$ ).

**Berkowitz et al.**<sup>49</sup> conducted a multicenter, 12-week, double-blind, placebo-controlled study to compare the activity and tolerability of mometasone furoate nasal spray, with that of beclomethasone and placebo in the alleviation of the signs and symptoms of PAR. A total of 491 patients,  $\geq 12$  years of age, with PAR confirmed by skin test reactivity to relevant allergens were enrolled in the study; of these, 476 were included in the efficacy analysis. After a one to two week lead-in period, patients were assigned to 12 weeks of mometasone 200 mcg once daily, beclomethasone 168 mcg twice daily, or placebo.

The primary assessment variable was the mean change from baseline in total nasal symptom scores (TNSS) derived from patient diaries during days 1-15 of treatment. Both mometasone and beclomethasone were more active than placebo for this variable ( $p < 0.01$ ). The mean percentage decrease from baseline was 21% for the mometasone furoate group, 23% for the beclomethasone group, and 13% for the placebo group, with no significant difference observed between the active treatment groups. Physician-evaluated mean percentage decrease in TNSS was significantly decreased for mometasone and beclomethasone compared to placebo at day 8 ( $p \leq 0.01$ ) and on the last visit ( $p = 0.01$ ). No significant differences were found between mometasone and beclomethasone.

### ***Comparison to fluticasone propionate***

**Mandl et al.**<sup>50</sup> conducted a 12-week, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study comparing once daily 200 mcg Nasonex with once daily 200 mcg fluticasone propionate (FP) and placebo for the treatment of PAR in a total of 550 patients 12 to 77 years of age. Primary efficacy variable was the mean change from baseline in total nasal symptom scores from patient diaries over days 1-15.

Results showed that both active treatment groups were significantly more effective than placebo ( $p < 0.01$ ). Patient diary data indicated a mean percent reduction from baseline in total nasal symptom scores of up to 63% with mometasone, up to 60% with FP, and up to 39% with placebo throughout the remainder of the study. Based on patient- and physician-evaluated overall condition, Nasonex was significantly more effective than placebo at all time points ( $p < 0.01$ ) except the offset period (1 week post-treatment), and FP was also more effective than placebo ( $p < 0.05$ ) except for weeks 8 and 12 (physician evaluation) and the offset period.

## **b) Efficacy in the Treatment of Seasonal Allergic Rhinitis**

### ***Comparison to beclomethasone dipropionate***

The use of Nasonex Nasal Spray in the treatment and prophylaxis of seasonal allergic rhinitis was evaluated in several clinical trials. **Hebert et al.**<sup>51</sup> conducted a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study comparing Nasonex 100 mcg<sup>±</sup> and 200 mcg QD to beclomethasone dipropionate (BDP) 200 mcg<sup>†</sup> BID or placebo for 4 weeks in a total of 501 adult patients with moderate to severe SAR, who were symptomatic at screening and baseline.

Primary efficacy variable was the mean change in physician-evaluated total nasal symptom score from baseline to day 8. At day 8, the mean improvements from baseline (decrease in total nasal symptom score) were 53% for patients receiving Nasonex 100 mcg<sup>±</sup> QD, 59% for Nasonex 200 mcg QD, and 59% for BDP 200 mcg<sup>†</sup> BID, compared to a mean decrease of 34% in the placebo vehicle control group ( $p \leq 0.01$ ). Total nasal symptom score improved in all groups during the 4-week treatment period. Nasonex (100 mcg<sup>±</sup> and 200 mcg/day) and BDP were significantly more effective than placebo vehicle control in reducing total nasal symptom score at all time points ( $p \leq 0.01$ ), apart from the lower dose of Nasonex 100 mcg<sup>±</sup> QD at day 4.

All three active treatment groups were significantly superior to placebo in reducing total symptom score (a secondary efficacy variable) at all time points ( $p < 0.05$ ), in a pattern similar to total nasal symptoms. By the end of treatment, complete or marked relief was obtained in 77% of patients treated with Nasonex 100 mcg<sup>±</sup> QD, 79% with Nasonex 200 mcg QD, and 74% with BDP 200 mcg<sup>†</sup> BID, compared to 54% of placebo-vehicle controlled patients.

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<sup>†</sup> Recommended dosage for BDP is 168 to 336 mcg/day in two divided doses for patients  $\geq 12$  years old

<sup>±</sup> Recommended dose for Nasonex in patients  $\geq 12$  years of age for treatment of nasal symptoms of SAR and PAR is two sprays (50 mcg of mometasone furoate/spray) in each nostril once daily (total daily dose of 200 mcg).

### c) Efficacy in the Prophylaxis of SAR

#### *Comparison to Beclomethasone Dipropionate*

**Graft et al.**<sup>52</sup> conducted a randomized, double-blind, placebo-controlled study in SAR patients prior to the onset of the fall ragweed season. Approximately 4 weeks prior to the fall allergy season, a total of 349 patients with a clinical history of moderate to severe SAR, but without symptoms at baseline were randomized to receive 8 weeks of treatment with Nasonex 200 mcg QD, BDP 168 mcg BID, or placebo. The use of nasal, oral, and ocular decongestants or glucocorticoids, and oral antihistamines was prohibited during the 8-week study period.

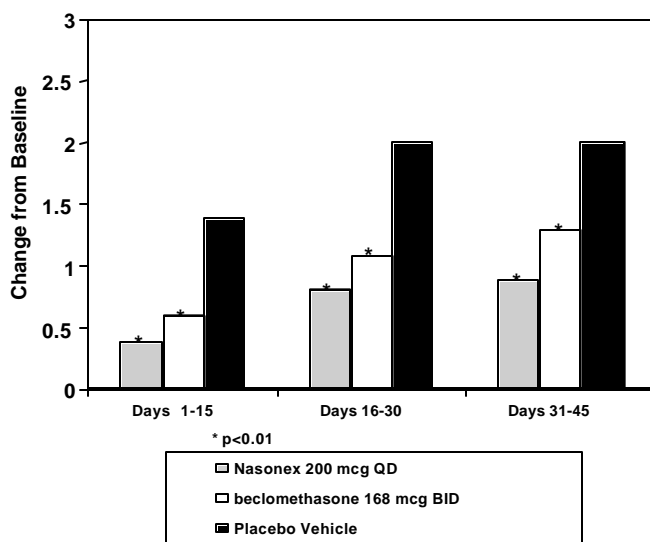
Efficacy was measured by the proportion of days with “minimal” symptoms, time to symptoms, and symptom scores, based on prophylactic treatment begun approximately 4 weeks prior to allergy season compared to 4 weeks during the allergy season. Both active treatments were determined to be statistically superior to placebo in preventing symptoms ( $p \leq 0.01$ ). Results showed that patients treated prophylactically with either active treatment had a significantly higher proportion of days with minimal symptoms during the ragweed season, than patients given placebo ( $p \leq 0.01$ ). Nasonex was significantly more effective than BDP\* and placebo during the prophylactic period, with significantly lower mean symptom scores prior to the onset of ragweed season than either BDP\* ( $p = 0.05$ ) or placebo ( $p = 0.01$ ). During the pollen season, both active treatments were significantly more effective than placebo ( $p < 0.01$ ), with a trend toward superiority of Nasonex over BDP in increasing the proportion of minimal symptom days that did not reach statistical significance ( $p = 0.08$ ).

Additionally, both active treatment groups demonstrated a pattern of longer duration to the first occurrence of a non-minimal symptom day, than the placebo group. Patients treated with either active treatment did not experience symptoms until a median of 27 days after the start of the ragweed season, compared to 10.5 days for patients treated with placebo ( $p \leq 0.01$ ).

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\* BDP is not indicated for prophylaxis of SAR.

### Average Change in Nasal Symptom Scores from Start of Ragweed Season



As depicted above, total nasal symptom scores based on diary data were significantly lower in both active treatment groups than placebo group ( $p < 0.01$ ). Similar results were obtained for total nasal symptom scores on the basis of physician's visit data.

### Comparison to Budesonide

**Marazzi et al.**<sup>53</sup> conducted a randomized, multicenter, double-blind, double-dummy, active- and placebo controlled study to assess the safety and efficacy of prophylactic treatment with mometasone furoate 200 mcg administered once daily, versus budesonide 400 mcg<sup>†</sup> administered once daily, and placebo in 500 patients 12 to 75 years of age. Patients were to be clinically asymptomatic at entry, but skin test positive to relevant seasonal tree, grass, and/or weed aeroallergen, with moderate to severe symptom history. They must not exhibit perennial allergy. Treatment was initiated prophylactically, approximately four weeks before significant pollen was airborne.

Both mometasone furoate and budesonide prevented symptoms for a significantly higher proportion of days (81% and 82%, respectively) after the start of the allergy season, as compared with placebo (63%;  $p \leq 0.01$ ). Identical results were observed in a subset of patients treated prophylactically for 15 days or less. Both physicians' evaluation and the patients' diary data indicated that both active treatments were significantly superior to placebo in reducing nasal symptom scores ( $p < 0.01$ ). The median duration to the first day with more than minimal symptoms after the start of the allergy season was significantly longer for either active treatment (26 days for mometasone, 34 days for budesonide) than for placebo (9 days;  $p < 0.01$ ).

<sup>†</sup> The recommended dosage of budesonide in the United States is 256 mcg/day in patients  $\geq 6$  years of age.

#### d) Efficacy in the Treatment of Nasal Polyps

Two studies<sup>24, 25, 29, 30</sup> were performed to evaluate the efficacy and safety of Nasonex Nasal Spray in the treatment of nasal polyps. These studies involved 664 patients with nasal polyps, 441 of whom received Nasonex Nasal Spray. These studies were randomized, double-blind, placebo-controlled, parallel-group, multicenter studies in patients 18 to 86 years of age with bilateral nasal polyps. Patients were randomized to receive Nasonex Nasal Spray 200 mcg once daily, 200 mcg twice daily or placebo for a period of 4 months. The co-primary efficacy endpoints were 1) change from baseline in nasal congestion/obstruction averaged over the first month of treatment, and 2) change from baseline to last assessment in bilateral polyp grade during the entire 4 months of treatment as assessed by endoscopy. Efficacy was demonstrated in both studies at a dose of 200 mcg twice daily, and in one study at a dose of 200 mcg once daily (see table below).

**Effect of Nasonex Nasal Spray in Two Randomized, Placebo-Controlled Trials  
in Patients with Nasal Polyps**

	<b>Nasonex 200 mcg qd</b>	<b>Nasonex 200 mcg bid</b>	<b>Placebo</b>	<b>P-value for Nasonex 200 mcg qd vs placebo</b>	<b>P-value for Nasonex 200 mcg bid vs placebo</b>
<b>Study 1</b>	N = 115	N = 122	N = 117		
Baseline bilateral polyp grade*	4.21	4.27	4.25		
Mean change from baseline in bilateral polyp grade	-1.15	-0.96	-0.50	< 0.001	0.01
Baseline nasal congestion**	2.29	2.35	2.28		
Mean change from baseline in nasal congestion	-0.47	-0.61	-0.24	0.001	< 0.001
<b>Study 2</b>	N = 102	N = 102	N = 106		
Baseline bilateral polyp grade*	4.00	4.10	4.17		
Mean change from baseline in bilateral polyp grade	-0.78	-0.96	-0.62	0.33	0.04
Baseline nasal congestion**	2.23	2.20	2.18		
Mean change from baseline in nasal congestion	-0.42	-0.66	-0.23	0.01	< 0.001

\* polyps in each nasal fossa were graded by the investigator based on endoscopic visualization, using a scale of 0-3 where 0 = no polyps; 1 = polyps in the middle meatus, not reaching below the inferior border of the middle turbinate; 2 = polyps reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate; 3 = polyps reaching to or below the border of the inferior turbinate, or polyps medial to the middle turbinate (score reflects sum of left and right nasal fossa grades).

\*\* nasal congestion/obstruction was scored daily by the patient using a 0-3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms.

There were no clinically relevant differences in the effectiveness of Nasonex Nasal Spray, 50 mcg, in the studies evaluating treatment of nasal polyps across subgroups of patients defined by gender, age, or race.

#### **e) Onset of Action**

The label indicates that patients with SAR have a demonstrated improvement in nasal symptoms within 11 hours after the first dose of Nasonex and maximum benefit achieved within 1-2 weeks after initiation of dosing (PI). Two studies evaluated the onset of action of Nasonex in 2 different environments (park setting and environmental exposure unit). Berkowitz et al.<sup>54</sup> found a significantly different mean change from baseline in total nasal symptom scores at 7 hours between Nasonex and placebo. Day et al.<sup>55</sup> found a significantly different mean change from baseline in total nasal symptom scores at 11 hours between Nasonex and placebo.

#### **f) Safety**

Nasonex has been found to be well tolerated and to have no systemic activity as measured by HPA-axis function in adults and with no growth suppression or HPA-axis suppression in children. The absorption of mometasone furoate (MF) was studied (**Brannan et al.**)<sup>56</sup> in adult men patients with rising doses administered by nasal inhalation (1, 2, 4 mg) compared with oral doses of MF (2, 4, 8 mg) and oral dexamethasone (0.2, 0.4, 0.8 mg). Systemic activity was based on hypothalamic-pituitary-adrenal axis function (HPA) during the 24-hour period after each dose. All treatments were well tolerated and no volunteer exhibited clinical symptoms of HPA suppression. In healthy male volunteers, Nasonex did not affect cortisol secretion, even up to 20 times the projected clinical dose.

Tolerability over the long term was reported by **Minshall et al.**<sup>57</sup> in a 12-month study of 200 mcg/day Nasonex in PAR patients. Nasal biopsy specimens were obtained from patients at baseline and after treatment. A total of 69 patients and 30 control subjects were recruited. Fifty-two patients and 24 normal controls completed the 12-month study. The nasal biopsy samples were evaluated in a blinded fashion by computerized image analysis, qualitative histologic examination and immunocytochemistry. Morphologic examination showed a decrease in focal squamous metaplasia, no change in epithelial thickness, and no sign of atrophy after treatment with Nasonex. The study demonstrated that long-term administration of Nasonex is not associated with adverse tissue changes in the nasal mucosa of patients with PAR. Additionally, treatment with mometasone reduced the extent of inflammatory cell infiltration, particularly eosinophils.

Two bioavailability studies evaluated the systemic exposure of Nasonex. The first<sup>58</sup>, which evaluated the absolute bioavailability of Nasonex, determined the absorption of mometasone to be *negligible*. The second study<sup>59</sup>, which utilized radiolabeled Nasonex, found *virtually no detectable drug in plasma*.

### g) Pediatric Use

An important issue with corticosteroids is their potential to suppress growth in children. Class labeling is required for nasal steroids, which indicates the potential for suppression of growth velocity in children. To test the impact of Nasonex on growth, a 1-year study of patients between 3 and 9 years of age with PAR was conducted to assess Nasonex 100 mcg/day versus placebo on growth (**Schenkel et al.**)<sup>47</sup> Each subjects' height was measured with a calibrated stadiometer at baseline and at 4, 8, 12, 26, 39, and 52 weeks. After one year of treatment, no suppression of growth velocity and standing height was seen in subjects treated with Nasonex, and mean standing heights were similar for both treatment groups at all time points. Treatment was well tolerated with no evidence of retardation of growth or suppression of HPA-axis function in PAR subjects as young as 3 years of age.\*

**Skoner et al.**<sup>60</sup> showed that intranasal BDP was associated with a reduced growth rate. The mean change in standing height after 1 year was 5.0 cm in BDP-treated subjects compared with 5.9 cm in the placebo-treated subjects. The difference in growth rates was evident as early as the 1-month treatment visit.

Systemic exposure and tolerability of Nasonex was examined in children aged between 3 and 12 years of age using HPA function by **Brannan et al.**<sup>61</sup>. In phase 1, children ages 6-12 years received Nasonex doses of 50, 100, or 200 mcg or placebo once daily for 7 days. In phase 2, children ages 3-5 years received Nasonex doses of 50, 100, or 200 mcg or placebo once daily for 14 days.

In phase 1, the mean plasma cortisol and 24-hour urinary free-cortisol concentrations of the Nasonex-treated and placebo groups were not statistically different. In phase 2, the plasma cortisol response to cosyntropin was not statistically significantly different from baseline values on day 7 or day 8. Nasonex was well tolerated by both the younger and older groups. Headache was the most frequently reported adverse event in both the placebo and Nasonex treated groups. The results indicate that 200 mcg Nasonex administered for up to 14 days in children with AR did not result in HPA-axis suppression in children ages 3-12 years.

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\* Controlled clinical studies have shown intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. The growth of pediatric patients receiving intranasal corticosteroids, including Nasonex Nasal Spray 50 mcg, should be monitored routinely (eg, via stadiometry). The potential of Nasonex to cause growth suppression in susceptible patients or when given at higher doses cannot be ruled out.

## **h) Efficacy in Nasal Congestion Associated with Allergic Rhinitis**

In an internet survey conducted with 2355 self-reported allergic rhinitis sufferers or parents of children with allergic rhinitis, eighty-five percent of those surveyed complained about congestion.<sup>62</sup> The discussion below focuses on several trials that used nasal stuffiness or congestion as a secondary endpoint for evaluation. These studies have also been discussed in the above sections under the respective subject.

### **PAR**

In **Mandl et al.**,<sup>50, 63</sup> the primary efficacy variable was the change from baseline in total AM plus PM diary nasal symptom score over the first 15 days of treatment. Additionally, stuffiness/congestion was assessed at day 15. Active treatment resulted in a significant reduction in both physician and patient assessed nasal stuffiness/congestion (46% vs. 30%,  $p < 0.01$  and 30% vs. 20%,  $p < 0.01$ , respectively). In this study, which also included fluticasone propionate (FP), there were no significant differences in congestion scores between the active treatments as assessed by patients. Mometasone furoate nasal spray (MFNS) was statistically superior to FP in improvement of physician-rated nasal congestion at day 29 and week 8 (53% vs. 45% and 56% vs. 48%, respectively;  $p = 0.04$ ). FP was not statistically superior to MFNS for any parameter at any time point. Results are shown below.

**Mean Percentage Decrease in Nasal Stuffiness at Day 15**

	<b>Placebo</b>	<b>Mometasone Furoate</b>	<b>Fluticasone Propionate</b>
<b>Patient assessment</b>	20	30*	31*
<b>Physician assessment</b>	30	46*	41*

\*  $p < 0.01$  vs. placebo

We are also aware of an **unpublished study**<sup>64</sup> which evaluated the efficacy and safety of mometasone furoate nasal spray (MFNS) in the treatment of patients with perennial rhinitis. Three hundred eighty seven patients participated in this randomized multicenter, double-blind, double-dummy, active- and placebo-controlled, parallel group study. Beclomethasone dipropionate (BDP) nasal spray (Beconase AQ<sup>®</sup>) was chosen as the active comparator. Primary efficacy variable was the mean change from baseline in total nasal symptom scores, which included nasal stuffiness, from patient diaries over days 1 to 15. Nasal stuffiness was also individually evaluated in patient diaries and by physician assessments.

Mean decreases in total nasal symptom scores achieved with both active treatments were significantly greater than those observed with placebo ( $p \leq 0.01$ ). Mean percent decreases in nasal stuffiness scores in patient diaries were as follows: MFNS 19%, BDP 26% and placebo 15%. Mean percent decreases in nasal stuffiness scores according to physician assessments were MFNS 38%, BDP 38% and placebo 29% ( $p$  values were not provided).

## **Onset of Action**

In the onset of action study by **Berkowitz et al.**,<sup>54, 65</sup> the primary efficacy variables were change from baseline in total nasal plus non-nasal scores, total nasal scores, and total non-nasal scores. The study was conducted in an outdoor (park) setting. Nasal stuffiness or congestion was studied as a secondary efficacy endpoint. The mean score at 7 hours for the nasal stuffiness/congestion endpoint showed significant superiority of mometasone furoate nasal spray over placebo in improving nasal stuffiness/congestion scores (1.9 vs. 2.2, respectively,  $p = 0.04$ ).

In the second onset of action study by **Day et al.**,<sup>55</sup> the primary efficacy variable was change in total nasal symptoms. This study was conducted in an Environmental Exposure Unit (EEU) and nasal stuffiness or congestion was evaluated as a secondary efficacy endpoint. In this study, Nasonex was significantly more effective than placebo in reducing congestion symptom scores at 11 hours post-dose ( $p = 0.03$ ).

## **SAR**

**Hebert et al.**<sup>51</sup> compared varying doses of Nasonex (100 mcg and 200 mcg) to beclomethasone dipropionate (BDP) in the treatment of SAR. The primary efficacy variable in this study was defined as the physician-rated mean change in total nasal symptom score from baseline to day 8. The study also had the physicians evaluate nasal stuffiness/congestion as an individual endpoint. Both doses of Nasonex (100 mcg and 200 mcg) and BDP 400 mcg demonstrated significant mean percent improvements from baseline versus placebo at day 8 and at endpoint for nasal stuffiness/congestion scores. At day 8, improvement in nasal stuffiness/congestion scores was 41%, 52%, 45%, and 28% respectively ( $p \leq 0.01$ ). At endpoint, improvement in nasal stuffiness/congestion scores was 62%, 67%, 61%, and 45% respectively ( $p \leq 0.01$ ).

## **Polyposis**

Please refer to page 25: Section: D. Efficacy in Polyposis.

### **i) Off Labeled Use**

Nasonex has been studied in a variety of off-labeled uses. Among these are sinusitis, perennial non-allergic rhinitis (PNAR) and cough associated with SAR.

## **Sinusitis**

The FDA reviewed adjunctive treatment in acute sinusitis and Nasonex was not approved for this use.

**Meltzer et al.**<sup>66</sup> evaluated the use of mometasone as adjunctive treatment in acute sinusitis. Patients received either Nasonex 400 mcg twice daily<sup>†</sup> or placebo nasal spray for 21 days. All patients in the study also received Augmentin<sup>®</sup> 875 mg (amoxicillin 875 mg and clavulanic acid 125 mg) twice daily throughout the treatment period. The decrease in mean total symptom score of 50.5% in the Nasonex group through Day 15 was significantly ( $p = 0.01$ ) greater than the 44.4% decrease seen in the placebo group. Further improvements were seen in total symptom scores when Days 16-21 were compared to Days 1-15. The Nasonex patients displayed a 68.1% decrease in total symptom score compared to baseline for Days 16 through 21 which was significantly ( $p < 0.01$ ) greater than the 56.5% decrease in the placebo group.

The individual symptom scores for nasal congestion and facial pain were significantly ( $p \leq 0.01$ ) decreased in the Nasonex treatment group compared to the placebo treatment group over Days 1 to 15. All three inflammatory symptoms associated with swelling (headache, congestion, and facial pain) were significantly better relieved in the MFNS group compared to placebo during Days 16 through 21 ( $p \leq 0.01$ ).

**Nayak et al.**<sup>67</sup> also evaluated the effectiveness and safety of adjunctive treatment with Nasonex in patients with acute rhinosinusitis. Patients in the 21-day, randomized, double-blind, placebo-controlled study received 21 days of antibiotic treatment with Augmentin<sup>®</sup> 875 mg BID, and were randomized to receive Nasonex 200 mcg BID, 400 mcg BID, or matching placebo. Significant improvement in total symptom scores for both Nasonex groups compared to placebo was observed over the entire 21-day treatment period. There was a significant reduction in nasal stuffiness/congestion for patients treated with Nasonex 200 mcg BID or 400 mcg BID compared with placebo over Days 1-15 ( $p = 0.01$  and  $p = 0.025$ , respectively). Complete or marked relief was reported by 63% of Nasonex 200 mcg treated patients, 66% of Nasonex 400 mcg patients, and 55% of placebo-treated patients at day 21 of treatment.

## **PNAR**

**Lundblad et al.**<sup>68</sup> conducted an 11-week, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of mometasone furoate for the treatment of perennial-non-allergic rhinitis (PNAR). Investigators randomized 329 patients with a mean duration of PNAR of 9 years to receive mometasone 200 mcg daily or placebo. The primary efficacy variable was the improvement rate during the double-blind period with respect to the subjects overall evaluation of PNAR. Results for the primary efficacy variable, subject's overall evaluation of treatment, found numerically greater improvement rates in symptom scores in subjects treated with mometasone versus placebo in both the ITT (56% and 49%, respectively,  $p = 0.25$ ) and PP (58% and 47%, respectively,  $p = 0.07$ ) groups. The investigator's overall evaluation found significantly greater improvements from baseline symptoms scores in the mometasone treated patients over placebo treated patients in both the ITT (60% and 48%, respectively,  $p = 0.03$ ) and PP (62% and 46%, respectively,  $p = 0.01$ ) groups.

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<sup>†</sup> The usual recommended daily dose for prophylaxis and treatment of the nasal symptoms of seasonal allergic rhinitis and treatment of the nasal symptoms of perennial allergic rhinitis is two sprays (50 mcg) in each nostril once daily

### **Cough Associated with SAR**

**Gawchik et al.**<sup>69</sup> conducted a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the use of Nasonex for cough. A total of 245 subjects, 12 to 74 years of age, with a one year or greater history of seasonal allergic rhinitis with associated seasonal cough, were enrolled in the study. Subjects were randomized to receive either Nasonex Nasal Spray (n = 122) or placebo (n = 123) for 14 days. The mean change from baseline in daytime cough (reflected in PM ratings) was significantly improved in the Nasonex-treated group compared to placebo at all time points and in the repeated measures analysis (the predicted average at all time points) for the Efficacy population (n = 113;  $p \leq 0.029$  at Week 1). For the intent-to-treat (ITT) population (n = 122) the mean change at endpoint in daytime cough was significantly improved in the Nasonex group compared to the placebo ( $p = 0.049$ ). There were no significant differences between treatment groups for the mean change from baseline in nighttime cough (reflected in AM ratings). However, the mean changes in the Nasonex-treated group were consistently greater than in the placebo-group.

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(total daily dose of 200 mcg) in adults and children  $\geq 12$  years.

## **2.2 PROPOSED CLINICAL DISEASE MANAGEMENT SERVICES OFFERED**

### **Helping Patients through Communication and Education**

Using Internet technology, we have helped improve communication across the healthcare continuum. Schering's e-health services help managed care organizations, employers, and physicians give members, consumers, and patients valuable health information about maintaining good health as well as managing existing conditions to optimize outcomes.

**My Health Zone** helps our customers provide an informational non-branded Web resource which is an empowering, informative, and personal environment that encourages learning about general health and condition topics in a single source via their own Web sites. With My Health Zone, visitors will find the information they need to give them confidence in speaking with their health care providers and make better informed health related decisions. My Health Zone is tailored to put health seekers on the path to setting personal lifestyle goals and self-management treatment plans to facilitate better health outcomes. Visitors to My Health Zone may learn more about everything from managing cholesterol and diabetes to the challenges of beginning a new exercise program. The site was designed to help people document their journey to a healthier lifestyle and tailored to maximize the use of fun and informative interactive health tools, up-to-date content, and articles from credible sources.

The major components of My Health Zone include:

In-depth general health and wellness information within a medical library, which offers an up-to-date medical encyclopedia to help patients conduct research and answer basic medical questions on symptoms, treatments, and prevention of conditions. The illustrations in the encyclopedia present complex medical information in a visual medium that is easily understood.

Topic specific zones, such as the High Cholesterol Zone, Asthma Zone, and Allergy Zone for patients looking for information and tools to help manage specific chronic conditions. These zones offer features such as news articles and interactive and printable tools to promote self-management and compliance for chronic conditions.

The site provides a terrific opportunity for the entire family to access valuable information and guidance on specific issues and challenges. Specialized content in the Family Zone sections for children, teenagers, and parents means nearly everyone can benefit from My Health Zone's commitment to providing accurate information that's easy to understand.

In order to better serve the community, My Health Zone also features Spanish content, such as the Health Encyclopedia.

In addition to the medical components of the Web site, registered users have access to My Health Tracker, a set of personalized education tools to help manage and track day-to-day details of a user's health such as:

**Health Diary:** tracks symptoms and triggers through an easy to use calendar

**Nutrition Diary:** tracks calorie and fat intake for foods for any given meal

**Medication Diary:** tracks current medication taking habits with a refill reminder feature to help ensure compliance

**Diet and Exercise Calculators:** tracks calorie intake or calculates length of time to perform a specific exercise, such as aerobics or jogging, in order to burn calories from a meal

**Goals Planner:** helps users set personal health goals for weight, cholesterol, fat intake, calories, protein, carbohydrates, sugar, sodium, and glucose

**Brochures for Health** is a non-branded service that provides customized patient education materials to customers in electronic and traditional print formats. The Brochureware library contains more than 50 brochures covering a wide range of diseases and health and wellness topics. Topics include Allergy, Asthma-COPD, Cardiovascular, Diabetes, Hepatitis, and Health and Wellness.

Brochureware pieces are available in both print and electronic formats, offering great flexibility for use at the point of service or through the Internet. Schering-Plough provides customers with a private, password-protected Web site where they can order pieces through the customer's own print vendor. They also can order an electronic version to be forwarded by e-mail as well as download files for printing at a desktop or posting on a Web site.

Health plans, medical groups, employers, and pharmacies now use Brochureware materials. Customers order printed materials for distribution in the clinic, at health fairs, in health mailings, and through case managers. Electronic versions are downloaded for just-in-time printing at provider workstations. Brochureware materials are being distributed via employer e-mail as part of employer health and wellness campaigns.

The Brochureware library supports customer quality efforts, including HEDIS, EPSDT, and other quality performance measurements. Education content is derived from nationally recognized sources, including the NIH, National Heart Lung and Blood Institute, American Diabetes Association, and the National Cholesterol Education Program. Pieces are reviewed on a regular basis by Schering medical and regulatory experts to ensure they reflect current medical standards.

Brochureware does not include Schering product information. Customers receive their own pre-customized Brochureware web site free of charge. The sites are pre-populated with the customers' own logos, contact information and Web addresses for just-in-time ordering. The only costs to the customer are printing and shipping charges. Electronic materials are available free of charge.

**SchoolAsthmaAllergy.com** is an educational resource focused on Asthma and Allergy care that is designed primarily for school nurses and other caregivers of school-aged children. Schering-Plough has developed this site for school nurses, an often overlooked but vital link in the health care chain. Schering-Plough believes this resource can assist in the common goals of making asthma a manageable condition for kids. It is important to remember that between five and six million children have asthma in the United States. Asthma is a leading cause of missed school days, accounting for an estimated 10 million absences per year. This resource provides a variety of tools to assist in educating teachers, coaches, and administrators. In addition, there are sections specifically designed to help kids, teens, and parents better understand and manage their condition and communicate with their physician.

Additionally, Schering administers a patient assistance program. For more information please dial 1-800-656-9485.

### 3. PRODUCT VALUE AND OVERALL COST

There are clear benefits for a health plan to include Nasonex on its formulary. The addition of Nasonex introduces a powerful choice to prescribers for the treatment of the broadest population of allergic rhinitis patients. Nasonex is the only nasally inhaled steroid approved for the treatment and prophylaxis of seasonal allergic rhinitis, treatment of perennial allergic rhinitis and treatment of nasal polyps.

Nasonex demonstrates an excellent, well-documented, safety and tolerability profile.

- Nasonex clinical trials have found no detectable systemic exposure or HPA-axis suppression in adults and children.<sup>47, 56, 61, 70-75</sup>
- No clinically significant changes in ophthalmic examination concerning cataract formation or glaucoma were observed in two clinical studies of 12-week and 12-month duration, in which no cataracts and no significant difference from baseline in mean intraocular pressure were detected with the use of Nasonex in patients with perennial allergic rhinitis.<sup>76, 77</sup>
- In pediatric patients, clinical trials have confirmed that there is no detectable systemic exposure or suppression of HPA-axis function, as well as no suppression of growth.<sup>47, 61, 74, 75, 78</sup>

Nasonex has negligible systemic absorption. Two bioavailability studies evaluating the systemic exposure of Nasonex determined the absorption of mometasone to be negligible, with virtually undetectable drug plasma concentration (0.1%).<sup>7, 59, 79, 80</sup> Clinical relevance in treatment of allergic rhinitis is unknown.

Nasonex exhibited no nasal atrophy, as demonstrated in a 12-month clinical trial of which morphologic examination showed no change in epithelial thickness or ratio of epithelial cross-sectional area to length of basement membrane, an increase in percentage of ciliated intact columnar epithelium, and a decrease in focal squamous metaplasia after 12 months of treatment with Nasonex.<sup>57</sup> Clinical relevance in treatment of allergic rhinitis is unknown.

- In addition, a decrease in inflammation was confirmed by immunocytochemical analysis that demonstrated a significant reduction from baseline in epithelial and submucosal eosinophils and mast cells, after 12 months of treatment with Nasonex in patients with perennial allergic rhinitis ( $p < 0.001$ ).<sup>57</sup>

Nasonex has demonstrated superiority to fluticasone propionate nasal spray in overall product preference based on sensory attributes for scent/odor, taste, and after-taste in a randomized, double-blind, cross-over preference evaluation study in patients with allergic rhinitis, based upon a nasal spray evaluation questionnaire ( $p < 0.005$ ). Efficacy was not measured in this study.<sup>81</sup>

Schering-Plough introduced a scent-free and alcohol-free formulation of Nasonex. This formulation does not contain phenylethyl alcohol, a colorless liquid with a rose-like odor.<sup>1</sup> The original formulation of Nasonex Spray contained 0.25% w/w phenylethyl alcohol as a preservative. Studies evaluating the stability of this new formulation found that the removal of phenylethyl alcohol does not adversely effect the stability of the product if stored under recommended conditions as indicated in the product information sheet.

This dossier has presented clear evidence that Nasonex should be considered as a useful addition to the preferred drug listing for the treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis in patients aged 2 years and older, in the prophylaxis of the nasal symptoms of allergic rhinitis in patients aged 12 years, and older and treatment of nasal polyps in patients aged 18 years and older.

## **4. SUPPORTING INFORMATION**

#### 4.1 FORMULARY SUBMISSION CHECKLIST

A. SUBMISSION PROCESS	Yes	No
A.1 Have you met with [– –] staff to review the submission process?		
A.2 Have you agreed to the submission date with [– –]?		
A.3 Have you requested estimates to identify baseline characteristics of the populations of the health systems represented by [– –]?		
A.4 Have you included an explanation for any missing data? (Check yes if N/A)		
A.5 Have you submitted a copy of the dossier in both paper and electronic form?		
B. PRODUCT INFORMATION	Yes	No
B.1 Has a product description been provided for the product?	X	
B.2 Has a list of approved indications been given for the product?	X	
B.3 Has the place of this product in therapy been given for each indication?	X	
B.4 Have copies been provided of treatment guidelines for this product?		X
B.5 Have intermediate and final outcomes of therapy for this product been listed?	X	
B.6 Have you listed any co-prescribed drugs for this product by indication?	X	
B.7 Have you identified the comparator drugs for this product by indication?	X	
C. SUPPORTING CLINICAL INFORMATION	Yes	No
C.1 Have you identified all relevant clinical and other studies for the product and its comparators?	X	
C.2 Are copies of all summarized studies included in the submission package?	X	
C.3 Have you provided an electronic spreadsheet summary of all studies identified using the [– –] format?	X	
C.4 Have you included all relevant non-experimental studies for the product?	X	
C.5 Have you provided an electronic spreadsheet summary of all Non-experimental studies using the [– –] format?	X	
D. SUPPORTING ECONOMIC INFORMATION*	Yes	No
D.1 Have you identified all relevant pharmacoeconomic (PE) studies for the product?		X
D.2 Are copies of all summarized studies included in the submission package?		X
D.3 Have you justified the relevance of these PE studies for this population?		X
D.4 Have you provided an electronic spreadsheet summary of the PE studies?		X
D.5 Will a disease or care management strategy be employed with the introduction of this product?		X
D.6 Is documentation on this intervention program included in the submission?		X
E. ECONOMIC MODEL*	Yes	No
E.1 Are the model structure, data and assumptions transparent and clearly presented for a non-economist reader?		X
E.2 Is an unlocked spreadsheet version of the model included with the submission?		X

\* At this time, supporting economic information and an economic model are unavailable for Nasonex.

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### 4.3 APPENDIX A Summaries of published literature

#### a) Summary of Published Studies with Nasonex in Seasonal Allergic Rhinitis (SAR)

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments / n (all Nasonex doses were given QD)	Endpoints/Results
<p>Bronsky EA et al. (1997)<sup>82</sup> (28 day treatment period) August 1992 – October 1992 15 centers in the US</p>	<p>Phase II, randomized, multicenter, double-blind, parallel group dose-ranging, placebo-controlled.</p> <p>Evaluations made at screening and at days 1, 3, 7, 14, 21, and 28.</p>	<p>Efficacy: n = 474 (ages 18-65)</p> <ul style="list-style-type: none"> <li>• Patients symptomatic at baseline and screening with overall disease of <math>\geq 3</math> on 7 point scale, with combined nasal symptom score of <math>\geq 10</math> and nasal congestion plus one other nasal symptom each scored at least moderate <math>\geq 3</math>.</li> <li>• IgE-medicated hypersensitivity to appropriate seasonal allergen with wheal size <math>\geq 3</math>mm larger than saline control.</li> </ul>	<p>Nasonex 50 mcg/day (n = 96) 100 mcg/day (n = 95) 200 mcg/day (n = 98) 800 mcg/day (n = 95)</p> <p>or placebo (n = 95)</p>	<p><b>Primary efficacy:</b> Mean change from baseline in total and nasal symptom scores.</p> <ul style="list-style-type: none"> <li>• All doses of Nasonex demonstrated efficacy in symptom relief compared to placebo from day 7 on (<math>p \leq 0.05</math>).</li> <li>• The 50 mcg and 100 mcg doses had variable efficacy during the first week of treatment.</li> <li>• The 200 mcg dose was deemed the most appropriate.</li> <li>• No additional efficacy was observed in patients taking 800 mcg compared to 200 mcg.</li> </ul>
<p>Frieri M et al. (1998)<sup>27</sup> (28 days total treatment duration) March 1994-May 1995 One study center in the US</p>	<p>Phase III, randomized, double-blind, placebo-controlled crossover study.</p> <p>Treatment period of 14 days with either placebo or Nasonex, four week washout period, two week treatment with alternative treatment (placebo or Nasonex).</p> <p>Nasal provocation with ragweed antigen.</p> <p>Evaluations at baseline, day 15, and day 57.</p>	<p>Efficacy: n = 21, (18 years and older, mean age 5.8, range 26-47)</p> <ul style="list-style-type: none"> <li>• History of SAR to ragweed documented by positive response to skin prick test.</li> <li>• Asymptomatic at screening, baseline, and visit 14 (total nasal symptoms graded <math>\leq 2</math> and no single symptom, nasal or non-nasal, rated severe or moderate).</li> </ul>	<p>Nasonex/placebo 200 mcg QD (n = 11)</p> <p>or</p> <p>Placebo/Nasonex (n = 10)</p>	<p><b>Primary efficacy:</b> Nasal fluid cytokines. <b>Secondary efficacy:</b> Nasal cytology, nasal fluid histamine level, nasal symptoms .</p> <ul style="list-style-type: none"> <li>• There was a statistically significant early phase difference between Nasonex and placebo in nasal lavage histamine levels 30 minutes after nasal challenge. The mean value observed in placebo was 20.2 ng/ml, versus Nasonex 14.3 ng/ml (<math>p = 0.02</math>).</li> <li>• Mean nasal symptom scores and sneezing frequency were consistently lower with Nasonex than placebo.</li> <li>• Nasonex reduced late phase IL-6, IL-8 and eosinophils compared with pre-treatment.</li> </ul>

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments / n (all Nasonex doses were given QD)	Endpoints/Results
<p>Graft D et al. (1996)<sup>52</sup> (8 week treatment period) June 1994 – October 1994 9 centers in the US</p>	<p>Phase III, randomized, multicenter, double-blind, active and placebo controlled, parallel group.</p> <p>Study was conducted approximately 4 weeks pre- (prophylactic) and 4 weeks during ragweed season.</p> <p>Evaluations at baseline and at days 8, 22, 29, 36, 50, and 57 (also day 71 if required).</p>	<p>n = 330 Efficacy, n = 34 (ages 12 years and older)</p> <ul style="list-style-type: none"> <li>SAR documented by skin prick or intradermal test.</li> <li>History of SAR for at least two years.</li> <li>Clinically asymptomatic at screening and baseline.</li> </ul>	<p>Nasonex 200 mcg QD (n = 114)</p> <p>beclomethasone dipropionate (BDP) 168 mcg BID (n = 112)</p> <p>or placebo (n = 104)</p>	<p><b>Primary efficacy:</b> Proportion of minimal symptom days from the start of ragweed season to study completion.</p> <ul style="list-style-type: none"> <li>Both active treatments were significantly more effective than placebo in preventing symptoms (p = 0.01).</li> <li>Nasonex was significantly more effective than placebo (p = 0.01) and numerically more effective than BDP (p = 0.08) increasing the proportion of nasal symptom days.</li> <li>Survival analysis showed significant differences to first symptomatic day; median number of days was 27 for Nasonex subjects, 27.0 for BDP patients, and 10.5 for those receiving placebo (p &lt; 0.01).</li> </ul>
<p>Hebert JR et al. (1996)<sup>51</sup> (28 day treatment period) March 1993 – August 1993 19 international centers</p>	<p>Phase III, randomized, multicenter, double-blind, double-dummy, active- and placebo controlled.</p> <p>Evaluations made at screening and days 1, 4, 8, 15, 22 and 29.</p>	<p>n = 477 Efficacy, n = 501 (ages 18 years and older)</p> <ul style="list-style-type: none"> <li>History of SAR for at least two years.</li> <li>Symptomatic at screening and baseline.</li> <li>Positive response to prick test with at least one relevant seasonal allergen; wheal size ≥3mm than saline control.</li> </ul>	<p>Nasonex 100 mcg QD (n = 126)</p> <p>200 mcg QD (n = 126)</p> <p>Beconase 200 mcg BID (n = 126)</p> <p>or placebo (n = 123)</p>	<p><b>Primary efficacy:</b> Mean change in physician-evaluated total nasal symptom scores from baseline to day 8.</p> <ul style="list-style-type: none"> <li>Physician-rated nasal and total symptom scores, and global evaluation of overall condition and therapeutic response by physicians and patients showed the three active treatments were equally effective and significantly superior to placebo at most time points.</li> <li>At the end of treatment, complete or marked relief was obtained in 77% of patients with Nasonex 100 mcg/day, 79% with Nasonex 200 mcg/day and 74% with BDP compared with 54% of placebo controlled patients.</li> <li>Nasonex and BDP demonstrated improvements in physician-evaluated nasal stuffiness/congestion scores versus placebo (p ≤ 0.01).</li> </ul>

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments / n (all Nasonex doses were given QD)	Endpoints/Results
<p>Berkowitz R et al. (1999)<sup>54</sup> (7 day run-in period followed by single dose administration of medication in an outdoor park setting)</p> <p>Spring 1997 One center in the US</p>	<p>Single center, placebo-controlled, double-blind, randomized parallel group study.</p>	<p>Efficacy n = 235 (ages 12 to 60, mean age &lt; 35)</p> <ul style="list-style-type: none"> <li>• Female = 60%</li> <li>• Skin test positive for seasonal tree or grass allergens prevalent during April.</li> <li>• Total nasal symptom severity score of at least 6 (out of possible 12) with a nasal congestion score of at least 2 (on scale of 0-3) on 6 of the 14 (morning and evening) recording periods during a 7-day run-in before to treatment.</li> </ul>	<p>Nasonex 200 mcg QD (n = 119)</p> <p>or placebo (n = 116)</p>	<p><b>Primary efficacy:</b> Change from baseline in the total nasal symptom score.</p> <ul style="list-style-type: none"> <li>• Mean change in total nasal symptom scores was significantly different between treatment groups at 7 hours; this difference was maintained for the remainder of the study (p &lt; 0.05).</li> <li>• There was a significant difference in total nasal plus nonnasal symptom scores between Nasonex and placebo at five hours, which lasted the duration of the study (p &lt; 0.05).</li> <li>• Mean change in total non-nasal symptom scores was significantly different at hour 5; this difference was maintained for the remainder of the study (p = 0.04).</li> <li>• Overall patient assessment of therapeutic response revealed a significant difference between treatments (p &lt; 0.01).</li> </ul>
<p>Berkowitz RB et al. (1999)<sup>83</sup> (2 week treatment period)</p> <p>April 1994-June 1994</p>	<p>Randomized, multicenter, double-blind, placebo-controlled study.</p> <p>Evaluations at days 4, 8 and 15.</p>	<p>n = 201, n = 200 Efficacy (ages 12-59 years)</p> <ul style="list-style-type: none"> <li>• Patients required to have history of SAR for 2 ≥ years.</li> <li>• Patients were symptomatic at both screening and baseline.</li> </ul>	<p>Nasonex 200 mcg QD (n = 101)</p> <p>or placebo (n = 99)</p>	<p><b>Primary efficacy:</b> Onset of action based on symptom scores.</p> <ul style="list-style-type: none"> <li>• By 12 hours after initial dosage, 28% of patients in Nasonex group experienced clinically significant relief, compared with 13% of placebo group (p = 0.01)</li> <li>• By 72 hours, 64% of patients receiving Nasonex experienced at least moderate relief, compared to 40% of placebo group (p &lt; 0.01).</li> <li>• Both patient and physician ratings of symptom severity, response to treatment, and overall condition of rhinitis indicated significant (p &lt; 0.01) superiority of Nasonex over placebo.</li> </ul>

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments / n (all Nasonex doses were given QD)	Endpoints/Results
Meltzer EO et al. (1999) <sup>74</sup> (4 week treatment period) Spring 1996 20 centers in the US	Phase II, multicenter, double-blind, active- and placebo-controlled, parallel group.  Evaluations at days 4, 8, 15, and 29.	n = 679 (ages 6 to 11, mean age 9 years) <ul style="list-style-type: none"> <li>• Symptomatic during pollen season.</li> <li>• Positive response to skin prick test.</li> <li>• Female patients premenarchal.</li> </ul>	Nasonex 25 mcg QD (n = 137) 100 mcg QD (n = 135) 200 mcg QD (n = 133 ) beclomethasone dipropionate 84 mcg BID (n = 138)  or placebo (n = 136)	<b>Primary efficacy:</b> Physician evaluations of total nasal symptom scores at day 8. <ul style="list-style-type: none"> <li>• At day 8, all active treatments were significantly more effective than placebo (<math>p \leq 0.02</math>), and there were no significant differences between treatments.</li> <li>• There were no significant differences between Nasonex 25 mcg and placebo or between BDP and any Nasonex group at days 15 and 29.</li> <li>• By day 29, Nasonex 100 mcg was significantly more effective than Nasonex 25 mcg (<math>p = 0.03</math>), as was Nasonex 200 mcg (<math>p = 0.04</math>).</li> <li>• There were no significant differences between Nasonex 200 mcg and 100 mcg at any time point.</li> <li>• All doses of Nasonex were well tolerated and cosyntropin stimulation tests performed before and after treatment found no evidence of HPA-axis suppression.</li> </ul>
Meltzer EO et a. (1998) <sup>84</sup> (2 week treatment period) April – August 1997 One center in the US	Single center, double blind, randomized, parallel group, placebo controlled study.  Evaluations on days 8 and 15.	Efficacy: n = 121 (ages 12 to 65 years) <ul style="list-style-type: none"> <li>• Patients were to be symptomatic at time of trial.</li> <li>• Positive skin test to allergens within the previous 14 months.</li> </ul>	Nasonex 200 mcg QD (n = 80)  or placebo (n = 41)	<b>Primary efficacy:</b> Subjective and objective assessment of total nasal and total symptom scores. <ul style="list-style-type: none"> <li>• There was a significant difference in patients' mean total morning score assessments between treatments for both week one (<math>p = 0.02</math>) and week 2 (<math>p = 0.029</math>). Evening scores were also significantly different for week 1 (<math>p = 0.038</math>), but were not for week 2 (<math>p = 0.076</math>).</li> <li>• There was a significant difference in physician assessed total nasal symptoms at day 15 (<math>p = 0.024</math>), and in patient assessed total nasal symptoms (morning) at week one (<math>p = 0.047</math>).</li> <li>• At day 15, MFNS demonstrated significant reduction from baseline in nasal stuffiness/congestion scores versus placebo (<math>p = 0.022</math>).</li> </ul>

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments / n (all Nasonex doses were given QD)	Endpoints/Results
Agertoft L and Pedersen (1999) <sup>78</sup> (14 week treatment period) 1997	Randomized, double-blind, placebo-controlled crossover study.  Evaluations at start and end of each 2-week treatment period as assessed by knemometry (2-week washout period between treatments).	Efficacy: n = 22 (ages 7 to 12) <ul style="list-style-type: none"> <li>Patients required to have clinical diagnosis of allergic rhinitis .</li> <li>All children preadolescent.</li> </ul>	All patients received at intervals:  Nasonex 100 mcg QD Nasonex 200 mcg QD Budesonide 400 mcg QD  or Placebo	<b>Primary outcome:</b> Change in linear lower leg growth rate. <ul style="list-style-type: none"> <li>There were no significant differences in lower leg growth rates among the Nasonex 200 (0.95 ± 0.79 mm), budesonide 400 (0.73 ± 0.61 mm) or placebo (0.69 ± 0.70 mm).</li> <li>The growth rate of the group receiving Nasonex 100 (1.16 ± 0.67 mm) was greater than that for the group receiving placebo (p = 0.024) or budesonide (p = 0.033).</li> </ul>
Brannan MD et al. (1997) <sup>61</sup> Phase 1 (7 day treatment period) Phase 2 (14 day treatment period)	Randomized, evaluator-masked, placebo-controlled, multiple-dose, parallel group study.	Efficacy: n = 96 (ages 3 to 12 years) <ul style="list-style-type: none"> <li>Patients required to have history of chronic nasal stuffiness, nasal discharge or both.</li> <li>In Phase 1, patients ages 6-12 examined.</li> <li>In Phase 2, patients ages 3-5 examined.</li> </ul>	Nasonex 50 mcg QD (n = 24) 100 mcg QD (n = 24) 200 mcg QD (n = 24)  or placebo (n = 24)	<b>Primary efficacy:</b> HPA axis function. <ul style="list-style-type: none"> <li>In Phase 1, plasma cortisol concentrations were not statistically significantly different from baseline values on day 7 or day 8.</li> <li>In Phase 1, the mean plasma cortisol and 24-hour urinary free-cortisol concentrations of the Nasonex-treated and placebo groups were not statistically significantly different.</li> <li>In Phase I, plasma levels were undetectable in all plasma samples collected at 5 hours, 1 and 2 hours after dosing on days 1 and 7.</li> <li>In Phase 2, Nasonex patients demonstrated a normal cortisol response to cosyntropin stimulation on day 14.</li> <li>In Phase 2, mean plasma cortisol concentrations for Nasonex-treated groups were not statistically significantly different from the placebo group.</li> </ul>

## b) Summary of Published Studies with Nasonex in Perennial Allergic Rhinitis (PAR)

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments (Efficacy n)	Endpoints/Results
Drouin M et al. <sup>48</sup> (12 week treatment period) October 1993 – June 1994 24 centers in Canada and Europe	Phase III, randomized, multicenter, double-blind, double-dummy, active- and placebo-controlled, parallel groups.  Evaluations were made at screening, days 1, 8, 15, and 29, and at weeks 8 and 12.	Efficacy: n = 387, 427 (ages 12 years or older; 18 years or older in Germany, Belgium, and the Netherlands) <ul style="list-style-type: none"> <li>• PAR documented by a positive response to skin tests.</li> <li>• History of PAR of at least two years.</li> <li>• Symptomatic at screening and baseline.</li> </ul>	Nasonex 200 mcg QD (n = 129)  BDP 200 mcg BID (n = 134)  or placebo (n = 124)	<b>Primary efficacy:</b> Average change from baseline in total nasal symptom scores. <ul style="list-style-type: none"> <li>• There was no evidence of tachyphylaxis.</li> <li>• Based on patient diaries, both active treatments were significantly more effective than placebo (<math>p \leq 0.01</math>).</li> <li>• Based on physician evaluation, Nasonex was more effective than placebo at days 8 and 15, weeks 8 and 12, and endpoint (<math>p \leq 0.04</math>).</li> <li>• BDP was more effective than placebo at all timepoints except week 8 (<math>p &lt; 0.01</math>).</li> <li>• BDP and Nasonex were not significantly different from one another at any timepoint (<math>p \geq 0.16</math>).</li> </ul>
Mandl M et al. <sup>50</sup> (12 week treatment period, one additional week of observation) December 1994 – June 1995 25 centers in Canada, Latin America, and Europe	Phase III, randomized, multicenter, parallel group, double-blind, double-dummy, active- and placebo-controlled, parallel groups.  Evaluations were made at screening, baseline (day 1), days 8, 15, and 29, and weeks 8, 12 and 13.	Efficacy: n = 459, n = 550 (ages 12 years or older, and 18 years or over at sites 1, 4, and 11 in Canada, and sites 24 and 25 in the UK) <ul style="list-style-type: none"> <li>• PAR documented by positive skin test, or in absence of kin test, a diagnosed or suspected history of chronic, perennial non allergic rhinitis accompanied by nasal eosinophilia which had been corroborated by current nasal cytology.</li> <li>• History of corticosteroid responsive perennial rhinitis for at least two years.</li> <li>• Symptomatic at screening and baseline.</li> </ul>	Nasonex 200 mcg QD (n = 154)  Fluticasone propionate 200 mcg QD (n = 157)  or placebo (n = 148)	<b>Primary efficacy:</b> Average change from baseline in total AM plus PM diary nasal symptom scores over the first 15 days of treatment. <ul style="list-style-type: none"> <li>• In general, all three groups demonstrated an improvement in symptoms as assessed by both the patient and physician.</li> <li>• Based on patient diaries, both active treatments were significantly more effective than placebo (<math>p &lt; 0.01</math>); this difference was maintained throughout the study, including the offset period (<math>p \leq 0.01</math>).</li> <li>• Based on physician evaluations, both active treatments were significantly more effective than placebo (<math>p &lt; 0.01</math>).</li> <li>• Based on patient- and physician- overall evaluations, Nasonex was significantly more effective than placebo at all time points (<math>p &lt; 0.01</math>), except the offset period.</li> <li>• Active treatment resulted in a significant reduction in both physician and patient assessed nasal stuffiness/congestion (<math>p &lt; 0.01</math>).</li> </ul>

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments (Efficacy n)	Endpoints/Results
<p>Minshall E et al. (1998)<sup>57</sup> (One year treatment period)</p> <p>3 centers in the UK</p>	<p>Multicenter, open-label, uncontrolled trial.</p>	<p>n = 69 patients, n = 30 normal controls (Ages 18 or older, mean 30 years)</p> <ul style="list-style-type: none"> <li>• History of mild to moderate PAR of at least one year.</li> <li>• Symptomatic at screening and baseline.</li> <li>• Positive response to skin prick test.</li> <li>• Patients with moderately severe to severe SAR were excluded or not subject to biopsy during allergy season.</li> </ul>	<p>Nasonex 200 mcg QD (n = 52) “patients”</p> <p>or placebo (n = 24)</p>	<p><b>Primary outcome:</b> Changes in histopathologic features of nasal biopsies.</p> <ul style="list-style-type: none"> <li>• Morphologic examination of nasal biopsy specimens showed a decrease in focal metaplasia, no change in epithelial thickness, and no sign of atrophy after treatment with Nasonex.</li> <li>• Immunocytochemical analyses of nasal biopsy specimens obtained before and after treatment revealed a significant decrease in major basic protein-positive eosinophils and tryptase-positive mast cells in the epithelium and lamina propria after treatment.</li> <li>• Nasonex appeared to attenuate the inflammatory process by reducing the extent of the inflammatory cell infiltration, particularly of eosinophils.</li> <li>• Long-term administration of Nasonex is not associated with adverse tissue changes in the nasal mucosa of patients with PAR.</li> </ul>

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments (Efficacy n)	Endpoints/Results
<p>Schenkel E et al. (2000)<sup>47</sup> (One year treatment period)</p> <p>10 treatment centers in the US</p>	<p>Phase III, Randomized, placebo-controlled, double-blind, multicenter study.</p> <p>Intent to treat analysis .</p> <p>Evaluations made at baseline, and weeks 4, 8, 12, 26, 39, and 52 weeks.</p>	<p>n = 98 (3 to 9 years old, mean 6.4)</p> <ul style="list-style-type: none"> <li>• Patients no greater than stage 1 on Tanner Classification of Sexual Maturity.</li> <li>• Boys &lt;9.5 years and girls &lt;9 years at baseline; girls had to be premenarchal.</li> <li>• Skeletal ages within two years of actual age.</li> <li>• Height within the 5<sup>th</sup> and 95<sup>th</sup> percentile at baseline and between 3-24 months before screening.</li> <li>• One year history of PAR that required treatment within past 12 months, and positive response to skin test.</li> </ul>	<p>Nasonex 100 mcg QD (n = 49)</p> <p>or placebo (n = 49)</p>	<p><b>Primary outcome:</b> Change in standing height as measured by stadiometer at baseline and evaluations.</p> <p><b>Secondary outcome:</b> Cosyntropin stimulation.</p> <ul style="list-style-type: none"> <li>• Mean height was similar for both groups at all time points (<math>p \geq 0.20</math>).</li> <li>• There was no significant difference in the rate of growth between groups (<math>p = 0.80</math>).</li> <li>• For the primary outcome, both groups were similar at all timepoints except weeks 8 and 52; for both these points, mean increase in height from baseline was significantly greater in the Nasonex group.</li> <li>• All 38 patients enrolled in the cosyntropin stimulation portion of the study had a normal response at all time points; there was no evidence of HPA-axis suppression in the Nasonex treatment group at any time point.</li> <li>• After 1 year of treatment, no suppression of growth was seen in subjects treated with Nasonex, and mean standing heights were similar for both treatment groups at all time points.</li> </ul>

c) Summary of Unpublished Studies with Nasonex in Nasal Polyps

Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments / n	Endpoints/Results
<p>Small et al.<sup>29, 30</sup> (4 Month treatment period) June 2001 – March 2003 44 centers in 10 countries</p>	<p>Phase III, randomized, multicenter, double-blind, placebo-controlled 3 arm study consisting of a 14 day single-blind, placebo Run-in period followed by 4 months of double-blind treatment.</p> <p>Evaluations made at screening and at day 1, week 1 and months 1, 2, 3, and 4.</p>	<p>Efficacy: n = 347 (ages 18-81, mean age 47.5)</p> <p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>Subjects must have had a diagnosis of bilateral nasal polyps at the Screening and Baseline Visits. For each side (right and left), the nasal polyps as assessed by the investigator must have been Grades 1, 2 or 3.</li> <li>Clinically significant nasal congestion/obstruction must have been present with an AM instantaneous score = 2 for each of the last seven days of the 2 week run in period.</li> <li>Asthmatic subjects were included provided they had a documented FEV<sub>1</sub> of = 80% of the predicted within the past 6 months and did not have an exacerbation of their asthma within the past 30 days. Asthmatic patients receiving treatment with an inhaled corticosteroids must have been on a moderate stable dose regimen not exceeding 840 mcg of BDP per day or equivalent for at least one month prior to screening and must have remained stable throughout the study.</li> </ul>	<p>Nasonex 200 mcg QD AM (n = 112) 200 mcg BID (n = 121)</p> <p>or placebo (n = 111)</p>	<p><b>Co-Primary efficacy:</b> Change from baseline in congestion/obstruction averaged over the first month of the Treatment Period and Change from baseline to endpoint in the bilateral polyp grade.</p> <ul style="list-style-type: none"> <li>Nasonex 200 mcg BID was statistically superior to placebo with respect to congestion/obstruction during the entire 4 months of treatment (<math>p \leq 0.001</math>), and Nasonex 200 mcg QD AM was statistically superior to placebo at all time intervals starting at Week 2 (<math>p \leq 0.004</math>). Nasonex 200 mcg BID demonstrated significantly greater mean decreases from baseline than Nasonex 200 mcg QD AM at the primary time interval of 1 month (<math>p = 0.039</math>) and many other selected time intervals.</li> <li>Both twice and once daily dosing of Nasonex demonstrated statistically significant superiority over placebo with respect to bilateral polyp grade at Endpoint (<math>p = 0.011</math> and <math>p &lt; 0.001</math>, respectively), the primary time interval, as well as at most monthly visits.</li> </ul> <p><b>Secondary efficacy:</b> Change from baseline in loss of smell, Nasonex 200 mcg BID was statistically superior to placebo at 1 month (<math>p = 0.0396</math>), the primary time interval, and at most other time intervals.</p> <ul style="list-style-type: none"> <li>Nasonex 200 mcg QD AM was statistically significantly superior to placebo during the entire 4 month of treatment (<math>p = 0.019</math>).</li> <li>Anterior rhinorrhea and postnasal drip were observed to be statistically superior over placebo with Nasonex 200 mcg QD AM at all time intervals during the study (<math>p = 0.042</math> and <math>p &lt; 0.001</math>, respectively), and with Nasonex 200 mcg BID starting at week 2 (<math>p &lt; 0.001</math> and <math>p = 0.007</math>, respectively).</li> </ul> <p style="text-align: right;"><b>Continued on next page</b></p>

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Citation/ Duration/ Dates	Study Design	Patients/Study Criteria	Treatments / n	Endpoints/Results
Small et al. <sup>29, 30</sup>		<p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Sinus or nasal surgery within past 6 months/3 or more nasal surgeries .</li> <li>• Any surgical procedure that prevents accurate grading of polyps per protocol.</li> <li>• Subjects with presumed fibrotic polyps.</li> <li>• Complete (or near complete) nasal obstruction.</li> <li>• History of SAR within last two years</li> <li>• Ongoing rhinitis medicamentosa.</li> <li>• Dyskinetic ciliary/Kartagener’s syndrome.</li> <li>• Treated with intranasal steroids within last 2 weeks before screening.</li> <li>• Nasal septal deviation needing corrective surgery .</li> <li>• Nasal septal perforation.</li> <li>• Used investigational drug within 30 days prior to screening.</li> <li>• Ongoing respiratory tract infection.</li> </ul>		<ul style="list-style-type: none"> <li>• Statistically significant superiority over placebo with respect to Peak Nasal Inspiratory Flow (PNIF) was observed with Nasonex 200 mcg BID at all time intervals ( p = 0.002) and with Nasonex 200 mcg QD AM at all time intervals starting at week 2 (p = 0.09).</li> <li>• A statistically significantly greater proportion of subjects treated with Nasonex 200 mcg BID was classified as improved (57.14%) compared to Nasonex 200 mcg QD AM (43.24%) and placebo (33.93%; p &lt; 0.001).</li> <li>• At all time intervals, both Nasonex treatment groups demonstrated a statistically significant improvement over placebo in therapeutic response as assessed by the investigator (p = 0.003).</li> <li>• No specific HQOL burden was found to be evident in this population.</li> <li>• Nasonex did not demonstrate an improvement in HQOL status in comparison to placebo using SF-36 scales and Work Productivity and Activity Inventory .</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Incidence of treatment emergent AE’s was similar in the three treatment groups: 49%, 49% and 55% of subjects in Nasonex 200 mcg QD AM, Nasonex 200 mcg BID and placebo respectively.</li> <li>• Majority of AE’s were considered by investigators to be unlikely related to study drug.</li> <li>• Most frequently reported treatment-emergent AE’s were upper respiratory tract infection, headache and epistaxis.</li> <li>• Most frequently reported AE was epistaxis: 6%, 12% and 4% of subjects treated Nasonex 200 mcg QD AM, Nasonex 200 mcg BID and placebo respectively.</li> <li>• No deaths or life threatening AE’s were reported.</li> <li>• Two subjects reported SAE’s during treatment period.</li> <li>• 10 Subjects discontinued treatment due to AE’s.</li> <li>• 7 Subjects interrupted treatment because of an AE.</li> </ul>

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<p>Stjarne et al.<sup>24, 25</sup> (4 Month treatment period) 25 June 2001 – 20 Jan 2003 22 centers</p>	<p>Phase III, randomized, multicenter, double-blind, placebo-controlled 3 arm study consisting of a 14 day single-blind, placebo Run-in period followed by 4 months of double-blind treatment.</p> <p>Evaluations made at screening and at day 1, week 1 and months 1, 2, 3, and 4.</p>	<p>Efficacy: n = 302 (ages 18-86, mean age 48.6) <b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>Subjects must have had a diagnosis of bilateral nasal polyps at the Screening and Baseline Visits. For each side (right and left), the nasal polyps as assessed by the investigator must have been Grades 1, 2 or 3.</li> <li>Clinically significant nasal congestion/obstruction must have been present with an AM instantaneous score = 2 for each of the last seven days of the 2 week run in period.</li> <li>Asthmatic subjects were included provided they had a documented FEV<sub>1</sub> of = 80% of the predicted within the past 6 months and did not have an exacerbation of their asthma within the past 30 days. Asthmatic patients receiving treatment with an inhaled corticosteroids must have been on a moderate stable dose regimen not exceeding 840 mcg of BDP per day or equivalent for at least one month prior to screening and must have remained stable throughout the study.</li> </ul> <p style="text-align: center;"><b>Continued on next page</b></p>	<p>Nasonex 200 mcg QD AM (n = 101) 200 mcg BID (n = 101)  or placebo (n = 100)</p>	<p><b>Co-Primary efficacy:</b> Change from baseline in congestion/obstruction averaged over the first month of the treatment period and change from baseline to endpoint in the bilateral polyp grade.</p> <ul style="list-style-type: none"> <li>Change from baseline in congestion/obstruction symptom score for both Nasonex 200 mcg BID and Nasonex 200 mcg QD AM were statistically significantly superior to placebo at Month 1 and Nasonex 200 mcg BID was statistically superior to placebo during the entire 4 months of treatment and to Nasonex 200 mcg QD AM at all time intervals starting at week 2.</li> <li>Neither dose was statistically superior to placebo with respect to bilateral polyp grade (p = 0.061) including endpoint (p = 0.078). Nasonex 200 mcg BID consistently demonstrated a numerically greater reduction in mean bilateral polyp grade compared to both placebo and Nasonex 200 mcg QD AM.</li> <li>In an additional analysis conducted due to slight differences at baseline, baseline polyp grade was added as a covariate to the model for the analysis of the change baseline in polyp grade. In the covariate analysis, Nasonex 200 mcg BID achieved statistical superiority (p = 0.039) at endpoint relative to placebo. Nasonex 200 mcg QD AM was not better than placebo in either analysis.</li> </ul> <p><b>Secondary efficacy:</b> For secondary symptom scores (loss of smell, postnasal drip, anterior rhinorrhea) Nasonex 200 mcg BID was statistically significantly superior to placebo at Month 1 (p = 0.049, p &lt; 0.001, p = 0.001) and most other time intervals, respectively.</p> <ul style="list-style-type: none"> <li>Nasonex 200 mcg QD AM was only statistically superior to placebo for anterior rhinorrhea (p = 0.02).</li> </ul> <p style="text-align: center;"><b>Continued on next page</b></p>

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Stjarne et al. <sup>24, 25</sup>		<p><b>Exclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>• Sinus or nasal surgery within past 6 months/3 or more nasal surgeries .</li> <li>• Any surgical procedure that prevents accurate grading of polyps per protocol.</li> <li>• Complete (or near complete) nasal obstruction.</li> <li>• History of SAR within last two years .</li> <li>• Ongoing rhinitis medicamentosa.</li> <li>• Dyskinetic ciliary/Kartagener’s syndrome .</li> <li>• Treated within last 2 weeks before screening with intranasal steroids.</li> <li>• Nasal septal deviation needing corrective surgery .</li> <li>• Nasal septal perforation.</li> <li>• Used investigational drug in 30 days prior to screening.</li> <li>• Ongoing respiratory tract infection.</li> </ul>		<ul style="list-style-type: none"> <li>• Statistically significant superiority over placebo with respect to PNIF and evaluation of therapeutic response was observed with Nasonex 200 mcg BID at all time intervals, and Nasonex QD AM at all time intervals starting as week 2 and month 1 for PNIF and therapeutic response, respectively.</li> <li>• A statistically significantly greater proportion of subjects treated with Nasonex 200 mcg BID were classified as improved compared to Nasonex 200 mcg QD AM and placebo.</li> <li>• Nasonex did not demonstrate an improvement in HQOL status in comparison to placebo using the SF-36 scales, Work Productivity and Activity Inventory (WPAI-SHP) and the generic treatment satisfaction questionnaire.</li> </ul> <p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Nasonex 200 mcg QD AM and Nasonex 200 mcg BID were well tolerated with no unusual or unexpected adverse events .</li> <li>• The incidence of treatment-emergent adverse events was similar across treatment groups.</li> <li>• Most frequently reported treatment-emergent AE’s were upper respiratory tract infection, headache and epistaxis.</li> <li>• The proportion of subject reporting these AE’s were similar across treatment except for epistaxis. Epistaxis was reported in: 15%, 6%, and 5% of subjects treated with Nasonex 200 mcg BID, Nasonex 200 mcg QD AM, and placebo respectively.</li> <li>• Six subjects reported serious adverse events during the 4-month treatment period, or within 30 days of completing or discontinuing from the study. All serious adverse events were considered unrelated to study treatment.</li> <li>• One subject discontinued randomized treatment because of AE’s; however, the AE was considered unrelated to study drug (placebo).</li> <li>• Seven subjects interrupted randomized treatment because of an AE.</li> </ul>

**d) Summary of Published Studies with Nasonex in assorted off-label usage**

Citation/ Duration/	Study Design	Patients/Study Criteria	Treatments / n	Endpoints/Results
<p>Nayak et al. (2002)<sup>67</sup> (21 day treatment period) 61 medical centers in US</p>	<p>Randomized, multicenter, double-blind, placebo-controlled.</p> <p>Patients recorded symptom scores recorded in patient dairies at baseline and throughout the treatment period.</p> <p>Patient and investigator evaluation of response to treatment performed on day 21.</p>	<p>Efficacy: n = 967 (ages 8-78)</p> <ul style="list-style-type: none"> <li>Patients aged 12 years or older who experienced symptoms that characterized acute sinusitis: (TSS ≥ 6, at least one nasal symptom was to be moderate or severe, purulent rhinorrhea present, limited coronal paranasal CT scan at the baseline showing evidence of rhinosinusitis in one or more sinuses).</li> </ul>	<p>Nasonex 200 mcg twice daily (n = 318)</p> <p>400 mcg twice daily (n = 324)</p> <p>or placebo (n = 325)</p> <p>All patients in the study received Augmentin® (ACP) 875 mg (amoxicillin 875 mg and clavulanic acid 125 mg) twice daily throughout the treatment period.</p>	<p><b>Primary efficacy:</b> Improvement in the mean total symptom scores (TSS) over Days 1-15.</p> <ul style="list-style-type: none"> <li>The addition of MFNS 200 mcg or 400 mcg BID to ACP treatment significantly improved (p &lt; 0.02) the mean TSS compared to placebo and ACP.</li> <li>Significant improvement in TSS for both MFNS groups compared to placebo was also observed over the entire 21-day treatment period.</li> <li>There was a significant reduction in nasal stuffiness or congestion for patients treated with MFNS 200 mcg BID or 400 mcg BID compared with placebo over Days 1-15 (p = 0.01 and p = 0.025, respectively).</li> <li>Complete or marked relief was reported by 63% of MFNS 200 mcg treated patients, 66% of MFNS 400 mcg patients, and 55% of placebo-treated patients.</li> <li>Patients receiving MFNS 200 mcg or 400 mcg reported significant improvement of TSS compared to placebo as early as Day 4.</li> </ul>

Citation/ Duration/	Study Design	Patients/Study Criteria	Treatments / n	Endpoints/Results
Meltzer et al. (2000) <sup>66</sup> (21 day treatment period) 29 medical centers	<p>Randomized, multicenter, double-blind, placebo-controlled.</p> <p>Patients recorded symptom scores recorded in patient dairies at baseline and throughout the treatment period.</p> <p>Patient and investigator evaluation of overall response to treatment performed on day 21.</p>	<p>Efficacy: n = 407 (ages 17-73)</p> <ul style="list-style-type: none"> <li>Patients aged 12 years or older who experienced symptoms that characterized acute sinusitis .</li> <li>History of sinusitis episodes separated by symptom free periods (at least 2 sinus infections that required antibiotic treatment per year, for the last two years .</li> </ul>	<p>Nasonex 400 mcg twice daily (n = 200)</p> <p>or placebo (n = 207)</p> <p>All patients in the study received Augmentin<sup>®</sup> 875 mg (amoxicillin 875 mg and clavulanic acid 125 mg) twice daily throughout the treatment period.</p>	<p><b>Primary efficacy:</b> Change from baseline in the mean total symptom scores for Days 1 through 15 as recorded in patient diary.</p> <ul style="list-style-type: none"> <li>Nasonex group experienced a significantly greater decrease in mean total symptom scores (TSS) versus the placebo group through day 15 (50.5% versus 44.4% respectively, (p = 0.01).</li> <li>Further improvements were seen in TSS when Days 16-21 were compared to Days 1-15. The MFNS treatment group displayed a 68.1% decrease in TSS compared to baseline for Days 16 through 21 versus the 56.5% decrease in the placebo group (p &lt; 0.01).</li> <li>The individual symptom scores for nasal congestion and facial pain were significantly (p ≤ 0.01) decreased in the Nasonex treatment group compared to the placebo treatment group over Days 1 to 15.</li> <li>Physician evaluation of total symptom scores showed a significant (p &lt; 0.01) decrease in the Nasonex group (68%) compared to the placebo group (61%) at Day 21.</li> <li>Sixty-two percent of patients treated with Nasonex reported complete or marked relief compared with 49% of patients who received placebo (p &lt; 0.05).</li> </ul>
Bloom et al. (2004) <sup>68, 85</sup> (2 four month studies)	Two randomized, double-blind, parallel group, multicenter studies.	<p>Study #1: n = 354 Study #2: n = 310</p> <p>Adults with bilateral polyposis and AM nasal congestion at least moderate during placebo run-in were enrolled.</p> <p>Polyp size was graded by nasal endoscopy.</p>	<p>Nasonex 200 mcg BID</p> <p>Nasonex 200 mcg QD</p> <p>or placebo</p>	<p><b>Primary Efficacy:</b> Changes in polyp size score at endpoint and congestion score over month 1.</p> <p>Study #1:</p> <ul style="list-style-type: none"> <li>Polyp size decreased with MFNS 200 mg BID (27%, p = 0.011) and MFNS 200 mg QD (33%, p&lt;0.001) versus placebo (17%).</li> <li>All symptoms and PNIF improved consistently and significantly over month 1 with both MFNS regimens.</li> </ul> <p>Study #2:</p> <ul style="list-style-type: none"> <li>Polyp size decreased numerically with MFNS 200 mg BID (25%, p = 0.078) versus placebo (16%).</li> <li>Congestion improved with both MFNS regimens (BID, 29% [p &lt; 0.001]; QD, 20% [p = 0.01]) versus placebo (8%) at month 1.</li> </ul>

Citation/ Duration/	Study Design	Patients/Study Criteria	Treatments / n	Endpoints/Results
Lunblad et al (2001) <sup>69</sup> (6 week treatment period) 16 Nordic medical centers	Phase III, Randomized, placebo-controlled, double-blind, multicenter study.  Intent to treat analysis .  Patients recorded symptoms scores on diary cards twice daily.  Physician evaluations made at days 0, 14 and 42 of treatment and at day 63 (the end of follow-up period).	Efficacy: n = 329 (ages 18-82) <ul style="list-style-type: none"> <li>Patients were required to show unspecific rhinitis symptoms of at least moderate degree for at least 4 days per week during the month before the study.</li> <li>Patients had to demonstrate a negative skin prick test prior to entering the study.</li> </ul>	Nasonex 200 mcg daily (n = 122)  or placebo (n = 123)	<b>Primary efficacy:</b> Improvement in subject's overall evaluation of treatment. <ul style="list-style-type: none"> <li>Numerically greater improvement rates in symptom scores were seen in subjects treated with mometasone versus placebo in both the ITT (56% and 49%, respectively, p = 0.25) and PP (58% and 47%, respectively, p = 0.07) groups.</li> <li>Investigator's overall evaluation found significantly greater improvements from baseline symptoms scores in the mometasone treated patients over placebo treated patients in both the ITT (60% and 48%, respectively, p = 0.03) and PP (62% and 46%, respectively, p = 0.01) groups.</li> </ul>
Gawchik et al. (2003) <sup>86</sup> (14 day treatment period) 11 medical centers in US	Randomized multicenter, double-blind, placebo-controlled, parallel-group study.	Efficacy: n = 245 (ages 12-74) <ul style="list-style-type: none"> <li>One-year history of SAR-associated cough.</li> </ul>	Nasonex 200 mcg daily (n = 122)  or placebo (n = 123)	<b>Primary efficacy:</b> Change in cough severity from the baseline until the end of the study. <ul style="list-style-type: none"> <li>At endpoint, the group treated with MFNS showed greater mean improvement in the daytime cough severity score compared with placebo (p = 0.049).</li> <li>The group treated with MFNS also showed greater mean improvements in nighttime relief of most symptoms attributable to SAR including congestion (p &lt; 0.05), nasal itching (p &lt; 0.05), and sneezing (p &lt; 0.01).</li> <li>Improvements in the mean nighttime severity scores for cough and for rhinorrhea showed trends in favor of MFNS treatment.</li> <li>The daytime overall symptom scores showed greater improvements with MFNS treatment compared with placebo over week 1, week 2, and endpoint (p ≤ 0.011). The nighttime overall symptom score showed greater improvement with MFNS treatment compared with placebo at endpoint (p = 0.028).</li> </ul>

