Summary Review for Regulatory Action

Date	May 26th 2010
From	Lydia Gilbert-McClain, MD, FCCP
Subject	Deputy Director Division Memorandum
NDA Supplement#	20-762/S-038
Applicant	Schering -Plough Corporation
Date of Submission	July 30, 2009
PDUFA Goal Date	May 31, 2010
Proprietary Name / Established (USAN) names	Nasonex® Nasal Spray Mometasone Furoate Monohydrate (Mometasone Furoate)
Dosage forms / Strength	Nasal Spray/50 mcg of mometasone furoate in each 100 microliter spray
Proposed Indication(s)	Treatment of nasal congestion associated with seasonal allergic rhinitis
Action/Recommended action for NME:	*Approval*
Material Reviewed/consulted Action package including:	**Names of discipline reviewers**
Medical Officer Review	Xu Wang, MD
Statistical Review	Feng Zhou, MS

1. Introduction

Nasonex® (mometasone furoate) Nasal Spray is approved for the treatment of nasal symptoms of allergic rhinitis in patients two years of age and older, prophylaxis of seasonal allergic rhinitis in patients 12 years of age and older, and the treatment of nasal polyps in adults 18 years of age and older. Schering-Plough submitted a supplemental NDA seeking a new indication for the treatment of nasal congestion associated with seasonal allergic rhinitis in patients two years of age and older. The PDUFA due date for this supplement is May 31, 2010. Support for the new indication is based on the conduct of new clinical studies that were performed by Schering-Plough. There are no new CMC, pharmacology, or toxicology issues and thus this summary review will only highlight the salient aspects of the clinical program that provide information related to the regulatory decision for this application.

2. Background

Nasonex® (mometasone furoate) Nasal Spray was first approved on October 1, 1997. Like other products approved for allergic rhinitis, the efficacy of Nasonex for the treatment of allergic rhinitis symptoms, was based on demonstration of improvement in allergic rhinitis symptoms using the standard total nasal symptom score (TNSS) which is comprised of the four nasal symptoms of runny nose, itching of the nose, sneezing, and nasal congestion. Efficacy was established based on the composite score, and the labeled indication is stated as "treatment of the nasal symptoms of allergic rhinitis" with the specific nasal symptoms described in the Clinical Trials section of the label.

Allergic rhinitis is triggered by airborne allergens which may impact on upper respiratory tract mucosa and lead to formation of specific IgE antibodies in susceptible hosts. Contact with either superficial mucosal mast cells, or basophils, or those found free in the nasal cavity, bearing specific IgE directed against the allergen, leads to degranulation of mast cells and the release of mediators such as histamine, leukotrienes, prostaglandins, heparin, or trypsin. These mediators not only have an immediate rapid reaction (e.g. histamine) but they may also exert a prolonged inflammatory reaction. The anti-inflammatory properties of corticosteroids are believed to play a more definitive role in affecting the pathophysiology of the disease and not merely to relieve the symptom cascade of the disease process as is the case with antihistamine products. As such, corticosteroids have generally been shown to work more effectively on the nasal symptom of congestion as opposed to anti-histamines.

Subsequent to the approval of Nasonex, Schering-Plough has presented results from post-hoc analyses of their original clinical trial data that suggested that Nasonex may have a substantially significant effect on nasal congestion sufficient to support a separate claim for nasal congestion. Since Nasonex belongs to the corticosteroid class of medications, there is biological plausibility that Nasonex could have an effect on nasal congestion associated with allergic rhinitis. Schering-Plough has used these post-hoc analyses to engage the Agency in discussions for advertising claims to promote nasal congestion as a separate prominent claim. However, the Agency did not allow separate claims for nasal congestion but did allow Schering-Plough to advertise nasal congestion in the context of the other nasal symptoms of allergic rhinitis. The Division informed Schering-Plough that a separate clinical program would be required if they wanted a separate claim for nasal congestion. To this end, Schering conducted three placebo-controlled trials in patients with seasonal allergic rhinitis that were designed to look specifically at nasal congestion as the primary endpoint, and to demonstrate efficacy for seasonal allergic rhinitis using the total nasal symptom composite score. Since Nasonex is currently approved for both seasonal and perennial allergic rhinitis, Schering-Plough was urged to consider conducting the nasal congestion program in both seasonal and perennial allergic rhinitis; however they declined to do so and chose to focus only on the seasonal allergic rhinitis population.

3. CMC/Device

There are no unresolved CMC issues. The product under consideration is the approved Nasonex Nasal Spray product.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were included in this submission. This is acceptable as the product is an approved product and the preclinical data have already been reviewed with the original NDA submission.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology of mometasone furoate has been well characterized in the clinical pharmacology program with the original NDA application, and no new clinical pharmacology data were presented or needed to be considered for this supplement.

6. Clinical Microbiology

Not applicable. The product is a non-sterile nasal spray and there are no new microbiology issues.

7. Clinical/Statistical- Efficacy

Three pivotal efficacy and safety studies were conducted in adult patients 12 years of age and older with seasonal allergic rhinitis. These three pivotal studies (PO5528, PO5529, and PO5583), were designed with nasal congestion as the primary efficacy endpoint and the total nasal symptoms score (TNSS) was evaluated as a key secondary efficacy. In addition to these pivotal studies in adults, Schering-Plough submitted study reports from several other studies where nasal congestion was explored as a secondary endpoint. There were no data submitted for these additional studies and the data were not requested since the three pivotal studies conducted to support the nasal congestion claim are sufficient for evaluation of this claim. There were no studies conducted in the pediatric population.

The three pivotal studies are displayed in the table below. All the studies are randomized double-blind placebo-controlled multicenter studies conducted in the U.S. The study treatment regimens in all three studies were the same (i.e. Nasonex two sprays/nostril qd [200 mcg/day] or placebo. The usual criteria for study entry and exclusion were followed for these studies. In all studies, the primary efficacy outcome was nasal congestion symptom and the endpoint was the change from baseline in the average morning and evening reflective (AM/PM PRIOR) nasal congestion symptom score (NCSS) on a scale of 0 (= none) to 3 (= symptom is hard to tolerate; cause interference with activities of daily living and/or sleeping) averaged over days 1 to 15. The average reflective morning and evening (AM/PM PRIOR) Total Nasal Symptom score (rTNSS) was the key secondary efficacy endpoint. The key secondary endpoint was analyzed using a sequential step-down approach. Additional secondary endpoints included assessment of the individual nasal symptoms (reflective and instantaneous) as well as an assessment of the overall assessment of the disease by the patient and by the investigator.

Table 1: Studies to Support the proposed Nasal Congestion claim in seasonal allergic rhinitis

Study	**Age (years) Mean (range)**	**Number of patients/study arm**	**Endpoints**
P05528	40.8 (13 -78)	Nasonex = 162 Placebo = 162	rNasal congestion score (primary) rTNSS (secondary)
P05529	37.9 (12 -72)	Nasonex = 176 Placebo = 175	Nasal congestion score (primary) rTNSS (secondary)
PO5583	38.6 (13 -69)	Nasonex = 168 Placebo = 165	Nasal congestion score (primary) rTNSS (secondary)

rNasal congestion score (NCSS) – was the average of the AM/PM PRIOR nasal congestion score assessed on a 0 to 3 scale
rTNSS is the average of the AM/PM PRIOR total nasal symptom score (nasal congestion/stuffiness, rhinorrhea[runny nose/nasal discharge or postnasal drip], itching of the nose, and sneezing) assessed on a 0 to 3 scale for each symptom (maximum score = 12)

The demographic characteristics and disease baseline assessment of the patients were fairly similar across the three studies. The patients had a mean age of 38.8 years and had a history of seasonal allergic rhinitis for at least 2 years. The majority of the patients were Caucasians, and were predominately female (66%).

In two of the studies (P05529 and P05583), patients treated with Nasonex Nasal Spray had a statistically significant improvement in both the nasal congestion score and the TNSS. In the other study (P05528) the nasal congestion score did not reach statistical significance however the effect size (0.11) was close (0.15) to that of the effect size for study P05529, and the instantaneous (AM NOW) congestion score was statistically significantly improved (effect size 0.15) compared to placebo. Results (reflective nasal congestion and TNSS scores) for studies P05529 and P05583 are shown in the Table 2.

Table 2: Nasal congestion and TNSS results for studies P05529 and P05583

Treatment (Patient Number)	Baseline § LS Mean *	Change from Baseline LS Mean *	Difference from Placebo LS Mean *	P value for NASONEX 200 mcg qd vs. placebo
Nasal Congestion score				
P05529				
NASONEX 200 mcg qd (N=176)	2.63	-0.64	-0.15	0.006
Placebo (N=175)	2.62	-0.49		
P05583				
NASONEX 200 mcg qd (N=168)	2.62	-0.71	-0.31	<0.001
Placebo (N=164)	2.60	-0.40		
TNSS				
P05529				
NASONEX 200 mcg qd (N=176)	9.60	2.68	0.83	<0.001
Placebo (N=175)	9.66	1.85		
P05583				
NASONEX 200 mcg qd (N=168)	9.39	3.00	1.27	<0.001
Placebo (N=164)	9.50	1.73		

The statistical and clinical review Conclusions and Recommendations section indicate that the data support the efficacy claim of nasal congestion associated with seasonal allergic rhinitis and I concur with their conclusions.

8. Safety

There were no new safety signals identified in the three new studies conducted with Nasonex. Like all nasally inhaled products, the main safety concerns include local irritation associated with nasal irritation and epistaxis. As a locally administered corticosteroid, concerns for

delayed wound healing, local infections (such as with *candida* species) and in rare instances nasal septum perforation are safety concerns. The safety profile seen in the three studies submitted did not reveal any findings that heighten those concerns and no additional safety assessments are warranted.

9. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not convened for this application. There are no issues that warrant discussion at an AC meeting.

10. Pediatrics

The Applicant is seeking approval of this indication in patients down to two years of age. The studies were conducted in patients 12 years of age and older. However although there were no studies conducted in the pediatric population under 12 years of age designed with nasal congestion as the primary efficacy endpoint, there are several other efficacy studies in the pediatric population with seasonal allergic rhinitis where efficacy was demonstrated for the TNSS and nasal congestion was assessed (albeit as a secondary endpoint). The efficacy findings in those studies are within the range of what is seen in the adult and adolescent studies and support the extrapolation of the efficacy results from these nasal congestion studies. There are no outstanding PREA commitments for the indication of seasonal allergic rhinitis. The application was presented at the PERC meeting on March 3rd, 2010. The plan is to approve this application down to the age of two years. The applicant already has a waiver for studies in patients less than two years of age because (a) seasonal allergic rhinitis does not exist in patients less than two years of age and (2) nasally inhaled corticosteroids are not safe for use in patients under two years of age.

11. Other Relevant Regulatory Issues

None

12. Labeling

The applicant submitted the package insert in the new Physician Labeling Format (PLR). The label was reviewed in consultation with DDMAC, DRISK and DMEPA. The labeling recommendations from the consults were incorporated into the label and conveyed to the applicant. There are no outstanding labeling issues regarding the package insert. The Patient Instructions for Use was revised in accordance with the recommendations from DRISK and the applicant has incorporated all of the recommendations in revised labeling submitted to the application. The carton and container labels submitted on July 30, 2009 are unchanged from previously approved carton and container labels. Finally, this application does not need or have a Medication Guide.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The regulatory action on this supplement for the proposed indication of nasal congestion associated with seasonal allergic rhinitis will be an approval.

- Risk Benefit Assessment

There were no new safety signals in the clinical trials submitted with this application. The risk benefit for the currently approved indications in allergic rhinitis and nasal polyps and the proposed new indication of nasal congestion associated with seasonal allergic rhinitis is acceptable.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

- Recommended Comments to Applicant

There are no deficiency comments to convey to the applicant as this supplement will be approved.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20762	SUPPL-38	SCHERING PLOUGH HEALTHCARE PRODUCTS INC	NASONEX NASAL SPRAY (MOMETASONE FUROATE)

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/s/

LYDIA I GILBERT MCCLAIN
05/26/2010