CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-203

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	October 15, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-203
Applicant Name:	MEDA Pharmaceuticals
Date of Submission:	August 15, 2008
PDUFA Goal Date:	October 15, 2008
Proprietary Name:	Astepro Nasal Spray
Established Name:	Azelastine hydrochloride
Dosage form:	Nasal Spray
Strength:	137 mcg in each 0.137 mL spray
Proposed Indications:	Relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older
Action:	Approval

1. Introduction

MEDA Pharmaceuticals submitted proposed labeling with this application to support approval of Astepro (azelastine hydrochloride) Nasal Spray for relief of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older. The proposed dose is 1 or 2 sprays per nostril twice daily. MEDA Pharmaceuticals originally submitted this 505(b)(1) application on July 30, 2007, for the relief of symptoms of SAR in patients 5 years of age and older, and for the relief of symptoms of vasomotor rhinitis (VMR) in patients 12 years of age and older. A non-approval action letter was issued on May 30, 2008, citing three deficiencies: (1) Submitted data were not adequate to support the VMR indication; (2) Submitted data were not adequate to support the SAR indication in patients 5 to 11 years of age; and (3) The submitted data were not adequate to support the [redacted] labeling claim for SAR. MEDA Pharmaceuticals requested a Formal Dispute Resolution (FDR) from the Office of Drug Evaluation II (ODE II) on July 1, 2008. A FDR meeting was held on July 28, 2008, with representation from ODE II and this Division. The ODE II issued a written response on August 7, 2008, stating that the SAR indication for ages 12 years and above can be approved, pending labeling agreement, while upholding the non-approval of the VMR indication, SAR indication for ages 5 to 11 years, and [redacted] labeling claims for SAR. This resubmission is consistent with the ODE II position that the application for the SAR indication for ages 12 years and older can be a Class I submission. This summary review provides an overview of the application, including materials submitted with the original application, and the reasoning behind the original non-approval action. This summary focuses on the efficacy and safety studies.

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2. Background

Azelastine is an antagonist of the histamine H1 receptor. Antihistamines are used for symptomatic treatment of various allergic diseases, such as allergic rhinitis, allergic conjunctivitis, and urticaria. MEDA Pharmaceuticals has an ophthalmic formulation of azelastine marketed in the United States under the trade name Optivar, and a nasal spray formulation of azelastine marketed in the United States under the trade name Astelin. Astelin was approved in November 1996 for SAR in patients 12 years of age and older, in February 2006 for SAR in patients 5 to 11 years of age, and in September 2000 for VMR.

There are many drugs approved for use in patients with allergic rhinitis, including H1 receptor antagonists, nasal corticosteroids, and the leukotriene receptor antagonist montelukast. The numbers of drugs approved for non-allergic rhinitis are limited. Flonase (fluticasone propionate) has a nonallergic rhinitis indication, and Astelin has a VMR indication. MEDA Pharmaceuticals originally intended to maintain the VMR indication for Astepro.

The major difference between Astepro and Astelin is that the former contains two additional excipients, sucralose and sorbitol, which are intended to mask the distinctive bitter taste associated with the azelastine drug substance. MEDA Pharmaceuticals wishes to market this sweetened formulation of azelastine nasal spray because Astelin's bitter taste that has apparently limited patient acceptance. The bitter taste is from the drug substance azelastine hydrochloride.

In the original application, the proposed indications and dosage and administration recommendations for various ages of Astepro were identical to Astelin. MEDA Pharmaceuticals planned to support approval of Astepro by demonstrating comparability of Astepro to Astelin, following the principle outlined in the Agency Draft Guidance on Allergic Rhinitis.[1] That approach failed as discussed in section 7c of this review.

3. Chemistry, Manufacturing, and Controls

The drug substance azelastine hydrochloride is a well known compound that is already approved in commercial ophthalmic and nasal spray products as mentioned above. Astepro is a 0.1% w/v solution of azelastine hydrochloride adjusted to a target pH of 6.4. The major difference between the currently marketed Astelin and the proposed Astepro is that the latter contains two additional excipients, sucralose at —— w/v and sorbitol at —— % w/v. These two excipients are added to sweeten the formulation and mask the distinctive bitter taste of azelastine. Sucralose is a novel excipient for a nasal spray. Sorbitol has been used in other nasal sprays, but at concentrations much lower than the concentration in Astepro. The drug substance source, manufacturing, and specifications are the same for Astelin and Astepro. Both products deliver 137 mcg azelastine hydrochloride per 0.137 mL actuation. The container and pump closure system used in Astepro is the same as in Astelin, and the spray characteristics of the two are similar.

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[1] Guidance for Industry. Allergic Rhinitis: Clinical Development Program for Drug Products. Draft Guidance. Available at www.fda.gov/cder/guidance.

The drug product specifications of the two are also similar. All manufacturing and testing facilities associated with this application have acceptable EER status. The submitted stability data indicate that Astepro can be stored at room temperature with an expiry of 24 months.

4. Nonclinical Pharmacology and Toxicology

A full toxicology assessment was submitted previously and reviewed under NDA 20-144 for Astelin. To support the two additional excipients, MEDA Pharmaceuticals submitted results from a 2-week intranasal toxicology study in dogs and a 6-month intranasal toxicology study in rats, comparing the effects of Astelin and Astepro. The submitted studies showed that both formulations have similar toxicity profiles in the nasal mucosa and the respiratory system. Both formulations cause slight irritation of the nasal mucosa, but the magnitudes of the effects are similar. There are no outstanding nonclinical pharmacology and toxicology issues.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for azelastine hydrochloride were addressed in the original NDA for Astelin. The applicant submitted results from one clinical pharmacology study (study MP 429) to assess the comparative bioavailability between Astelin and Astepro following a single dose. The study was conducted in 18 healthy male subjects ages 18 to 50 years. The results of the study showed that there was slightly lower exposure to azelastine and the major active metabolite, desmethyazelastine, for Astepro compared to Astelin. The mean azelastine Cmax was 200 pg/mL and 235 pg/mL for Astepro and Astelin, respectively, and the mean azelastine AUC was 4917 pg.hr/mL and 5903 pg.hr/mL for Astepro and Astelin, respectively. The numerical differences for desmethyazelastine for the two formulations were similar. The lower systemic exposure from Astepro compared to Astelin is supportive of systemic safety of Astepro, meaning that the systemic safety profile for Astepro is not expected to be worse than Astelin.

6. Clinical Microbiology

The final product is not sterile, which is acceptable for a nasal spray product. The manufacturing process is adequate from a microbiological perspective. The drug product contains benzalkonium chloride as an [redacted] b(4)

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program submitted consists of three pivotal studies. The relatively small clinical program is acceptable given that Astelin is an approved product and that the intent of the clinical program was to establish comparability of Astepro to Astelin. Table 1 summarizes the characteristics of these pivotal clinical studies that form the basis of the regulatory decision. The design and conduct of these studies are briefly described below,

followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Pivotal clinical studies

ID	Disease *Study type*	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
MP 430	SAR *Efficacy and safety* *Comparability*	2 weeks	12-83	A-S 1 spray BID A-S 2 sprays BID A 1 spray BID A 2 sprays BID Pbo 1 spray BID Pbo 2 sprays BID	139 146 137 138 137 138	2006	USA
MP 432	Allergic rhinitis Nonallergic rhinitis *Long term safety* *Comparability*	52 weeks (6 month Interim)	12-82	A-S 2 sprays BID A 2 sprays BID	281 278	On-going	Australia, Europe
[redacted]							

* A-S = Astepro Nasal Spray; A = Astelin Nasal Spray; Pbo = Placebo Nasal spray; MF = mometasone furoate nasal spray (Nasonex);
# Year study subject enrollment ended

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b. Design and conduct of the studies

Study MP 430 was randomized, double-blind, placebo- and active-controlled, parallel-group in design, conducted in patients 12 years of age and older with SAR. The study had a 7-day placebo run-in period followed by a 2-week double-blind treatment period. The primary efficacy endpoint was change from baseline in morning plus evening reflective total nasal symptom score (rTNSS: sum of runny nose, sneezing, itchy nose, and nasal congestion; each scored on 0-3 scale) averaged over 2 weeks of treatment. Secondary efficacy variables included the instantaneous recording of the same four symptoms (iTNSS) and the Rhinoconjunctivits Quality of Life Questionnaire (RQLQ). Safety assessments included recording of adverse events, vital signs, physical examinations, and clinical laboratory measurements. This study was designed to show comparability between Astepro and Astelin and was the subject of a Special Protocol Assessment (SPA). In the SPA letter (dated November 4, 2005), the Division generally agreed with the design of the study.

Study MP 432 was randomized, open-label active-controlled, parallel-group in design, conducted in patients 12 years of age and older with perennial allergic rhinitis and non-allergic rhinitis. The study had a 7-day screening period followed by a 52-week open label treatment period. Safety assessments included recording of adverse events, vital signs, and physical examination with a focused nasal examination. Efficacy was assessed by the Mini RQLQ.

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[redacted]

c. Efficacy findings and conclusions

The submitted clinical studies, along with the known findings of Astelin, are adequate to support the efficacy of Astepro for SAR in patients 12 years of age and older. The clinical studies do not support approval of Astepro for SAR in patients 5 to 11 years of age, and also do not support the VMR indication. MEDA Pharmaceuticals in the original application and during the FDR contended that Astepro should have indications and dosage and administration recommendations for various ages identical to Astelin. • MEDA Pharmaceuticals contention was based on their determination that the submitted data demonstrated comparability between Astepro and Astelin, and therefore, all indications and dosage and administration recommendations for various ages should be carried over from Astelin to Astepro. The Division disagreed that comparability between Astepro and Astelin had been demonstrated, and ODEII agreed with the Division at the FDR that comparability had not been shown. MEDA Pharmaceuticals subsequently modified its position and is now only seeking the SAR indication for patients 12 years of age and older. The sections below comment on the SAR indication for ages 12 years and above, which is the subject of the current resubmission, as well as the issues of comparability, data needed to support a SAR indication for ages 5 to 11 years, and the VMR indication for ages 12 years and older.

SAR in patients 12 years of age and older, and [redacted] b(4)

In study MP 430, the 2 spray doses of Astepro and Astelin were both statistically significantly superior to placebo for the primary efficacy endpoint, but the 1 spray dose of both products did not statistically significantly separate from placebo (Table 2). Secondary efficacy variables generally trended in a similar direction for both products and for both doses (data not shown in this review). This single study conducted in patients with SAR ages 12 years and above is sufficient to support efficacy in SAR for ages 12 years and older. The Agency typically relies on findings from replicate studies as substantial evidence of efficacy, but in this specific instance a single study is adequate because of previous findings with Astelin, and the fact that both Astelin and Astepro are solution formulations with similar container and closure systems and similar in vitro characteristics. The dosing recommendation of both 2 sprays and 1 spray can be carried over to Astepro. Although the data from this study shows that 1 spray of both formulations did not statistically significantly separate from placebo, the efficacy trends for both 2 sprays and 1 spray favored Astepro over Astelin (Table 2). There is no reason to believe that Astepro at 1 spray per nostril would not be efficacious in SAR, as previous placebo controlled studies have shown a statistically significant difference between Astelin at 1 spray per nostril twice daily versus placebo.

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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Summary Review- 1

Comment on Comparability:

The decision to approve the SAR indication for ages 12 years of older is based on the reasoning stated above and is not based on demonstration of comparability. For this specific decision one does not even need to conclude whether comparability of the two products has been demonstrated. Nevertheless, it is worth commenting on comparability because MEDA Pharmaceuticals originally concluded that comparability between Astepro and Astelin had been demonstrated through study MP 430. MEDA Pharmaceuticals stated that the SAR indication for the full age range and VMR indications should be carried over from Astelin to Astepro on the basis of this comparability. However, the Division concluded that comparability has not been established for reasons stated below.

To support comparability of Astepro and Astelin, MEDA Pharmaceuticals referred to the Agency Draft Guidance on Allergic Rhinitis.[2] The Draft Guidance mentions general paths for supporting approval of changes in formulation using a comparability approach, but the Draft Guidance does not define how comparability can be established. Also there is no precedence of accepting comparability as the basis of approval of a nasal spray product. In a meeting with MEDA Pharmaceuticals held on May 3, 2005, the Division agreed that a comparability approach based on a single clinical study may support approval of Astepro for SAR in patients 5 years of age and older and also for VMR. The Agency stated in the meeting that "demonstration of clinical comparability should be convincing" and "whether clinical comparability is demonstrated will be a review issue." The Draft Guidance on Allergic Rhinitis recommends demonstration of comparability in a single study using two doses of each formulation and demonstration of comparability of the dose-response curves. Study MP 430 failed to show a dose-response because the 1 spray dose, which is an approved dose for SAR, did not statistically separate from placebo (Table 2). Without demonstration of dose-response, comparability cannot be assessed. Therefore, study MP 430 has failed to show comparability between Astepro and Astelin.

Another approach to assess comparability of two nasal spray products is to use the principle outlined in another related Agency Guidance document.[3] This guidance is on the development of generic nasal spray products. This guidance requires that the two products be qualitatively and quantitatively the same, meaning that they both contain same active and inactive ingredients and the amounts of each be within 5%. Astepro and Astelin are qualitatively and quantitatively different because of the presence of two excipients in Astepro that are not present in Astelin; however, because these two are solution formulations with the same container and closure system and similar in vitro characteristics, one can assume that the differences in excipients will not impact the rate and extent of availability of the active moiety at the site of action on the nasal mucosa.

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[2] Guidance for Industry. Allergic Rhinitis: Clinical Development Program for Drug Products. Draft Guidance. Available at www.fda.gov/cder/guidance

[3] Guidance for Industry. Bioavailability and bioequivalence studies for nasal aerosol and nasal spray for location action. Available at www.fda.gov/cder/guidance

Therefore, the criteria of bioequivalence described for clinical study in the guidance document are not unreasonable to apply here as a test of comparability. The design and conduct of study MP 430 are similar to the study recommended in the guidance document and allows for such analyses. Our statistical team performed equivalence analysis for Astepro and Astelin, which shows that the two products fail the bioequivalence test (Table 3). The guidance document recommends testing at the lowest labeled dose to optimize sensitivity. In study MP 430 the lowest labeled dose, 1 spray each nostril twice daily, did not even statistically separate from placebo and should not be tested. Nevertheless, both the 1 spray and the 2 sprays doses were tested and both failed. For the 2 sprays dose, with which both Astelin and Astepro statistically significantly separated from placebo, Astepro tended to be numerically better than Astelin (Table 3).

It appears that adding the two excipients has changed the efficacy of azelastine. The efficacy of Astepro may be better than Astelin in treating SAR, but the efficacy of Astepro and Astelin is certainly not comparable these criteria.

Table 3. Equivalence analysis for the change from baseline of rTNSS* (study MP 430)

Treatment comparisons	Baseline Mean	Baseline Median
	90% CI for the ratio of means	90% CI for the ratio of means
Astelin and Astepro, 2 sprays	0.986, 1.466	0.986, 1.464
Astelin and Astepro, 1 spray	0.866, 1.324	0.867, 1.323
* To pass BE equivalence test the 90% CI must fall between 0.8 and 1.25		

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SAR in patients 5 to 11 years of age

Astepro could not be approved for SAR for ages of 5 and 11 years ' [redacted] (Table 1). The primary concern is the lack of clinical safety data. In the SPA letter (dated November 4, 2005) the Division stated that a "separate clinical safety program to support the safety of the reformulated product" will be needed. The applicant has conducted a separate clinical safety study, but the study did not include any patients between the ages of 5 and 11 years (Study MP 432, Table 1).

MEDA Pharmaceuticals contended in the original application that the submitted clinical program should be adequate to [redacted]

[redacted]

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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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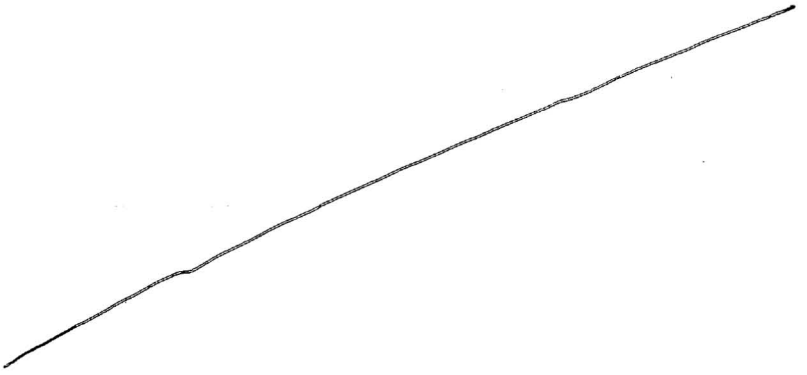

8. Safety

a. Safety database

The safety assessment of Astepro was based on the studies MP 430 and MP 432 (Table 1). A total of 564 patients 12 years of age and older were exposed to Astepro in these two studies 2 weeks and 6 months in duration. The overall safety database was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Astepro in patients 12 years of age and older. As mentioned above the application does not support safety for ages 5 to 11 years. There were no deaths in the clinical program. Serious adverse events were few and did not suggest a new safety signal. The majority of the adverse events were mild and generally similar between Astepro and Astelin. Common adverse events that occurred more in drug-treated groups compared to placebo in the 2-week study were bitter taste, epistaxis, headache, nasal discomfort, fatigue, and somnolence. In the long-term safety study, reporting of adverse events was similar. Nasal mucosal ulcerations and epistaxis were seen in both active treatment arms with similar frequency.

Addition of the two sweetening agents did not seem to mask the bitter taste of azelastine. In the 2 week study, bitter taste was the most common adverse event reported for both formulations, with a frequency of 7% and 6% with Astepro 2 sprays per nostril twice daily and 1 spray per nostril once daily, respectively, and 8% and 10% with Astelin 2 prays per nostril twice daily and 1 spray per nostril once daily, respectively. This is not surprising because bitter taste receptors are in the back of the tongue whereas sweet taste receptors are mostly at the tip of the tongue. A nasal spray formulation drips to the back of the tongue and does not reach the tip of the tongue in any substantial amount.

(12 years of age and older) with vasomotor rhinitis (VMR). Available at: http://ctr.gsk.co.uk/Summary/Fluticasone_furoate/studylist.asp

[11] Product label for Flonase (fluticasone propionate) Nasal Spray, 50 mcg

[12] Product labels for Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, and ProAir HFA Inhalation Aerosol.

c. REMS/RiskMAP

REMS and RiskMAP were not deemed necessary for Astepro. Other oral or nasal antihistamines or any spray products for allergic rhinitis do not have REMS or RiskMAP.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Azelastine is not a new molecular entity. Antihistamines, including nasal antihistamines, are a well studied drug class, and efficacy and safety of this class of drug, including azelastine, are well understood. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

This NDA does not trigger PREA because there is no new active ingredient, no new indication, no new dosage form, no new dosing regimen, or no new route of administration. The applicant has a reasonable pediatric development plan for azelastine nasal spray. During approval of the Astelin supplement (NDA 20-114, February 17, 2006) for 1 spray per nostril twice daily dosing for SAR, studies in children 2 years of age and older were deferred, and studies below 2 years of age were waived. The Division has taken the position that SAR does not occur in children below 2 years of age. Although the lower age cut-off is somewhat arbitrary, there is literature to support the lower age bound (J Allergy Clin Immunol 2000; 106:832). The deferred pediatric studies will adequately address all pediatric drug development for azelastine nasal spray down to the age of 2 years.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was requested for this application because azelastine nasal spray is a well studied product, and the two clinical studies conducted with Astepro were fairly routine standard studies. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There were 3 investigators with significant equity interest in MEDA Pharmaceuticals or its predecessor. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consult reviews received from DDMAC.

12. Labeling

a. Proprietary Name

With the original NDA, MEDA Pharmaceuticals proposed the trade name —— for this product. DMEDP reviewed that trade name and found it unacceptable. MEDA Pharmaceticals submitted two additional trade names, / —— and / ——, during the original NDA review. Both of these names were not acceptable to DMEDP. The problem with these trade names is that the root name for the product is the same, and the suffix contains an abbreviation that does not convey any specific meaning. Subsequently the applicant submitted two other trade names, Astepro and ——, also during the original NDA review. With this resubmission, MEDA Pharmaceuticals submitted the trade name Astepro. DMEDP finds this name acceptable. The name was also found to be acceptable to DDMAC from a promotional perspective. b(4)

b. Physician Labeling

With the original NDA, MEDA Pharmaceuticals submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other products of this class. The label was reviewed by various disciplines of this Division, and by DDMAC, and DMEDP, during the original NDA review. Various changes to different sections of the label were recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. During the original NDA review, MEDA Pharmaceuticals agreed to remove the VMR indication, and the SAR indication for ages 5 to 11 years, but at the same time attempted to request a FDR with the Office of New Drugs. The FDR was not accepted because there was no regulatory action to dispute. The Division and MEDA Pharmaceuticals were unable to come to a clear agreement about the removal of the ——— claim for SAR. Therefore, there was no agreed upon label at the time of the previous action. With the resubmission, MEDA Pharmaceuticals submitted a label with only the SAR indication for ages 12 years and older, and has removed the ——— claim for SAR. The label was again reviewed by various disciplines of this Division. The Division and MEDA Pharmaceuticals have agreed to the final version of the label. b(4)

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, DDMAC, and DMEP, and the last version was found to be acceptable.

d. Patient Labeling and Medication Guide

The patient instructions for use was reviewed by various disciplines of this Division, and DSRCS, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has submitted adequate data to support approval of Astepro for the relief of symptoms of SAR in patients 12 years of age and older. The action on this application will be Approval.

b. Risk Benefit Assessment

The overall risk and benefit assessment of Astepro supports its approval for relief of symptoms of SAR in patients 12 years of age and older without any specific restrictions. The submitted clinical study showed efficacy in SAR patients ages 12 years and older, and the safety profile was acceptable for this age group. The major safety findings of clinical concern were somnolence, fatigue, epistaxis, and nasal mucosal ulcerations. Sedation manifesting as somnolence and fatigue is common with some antihistamines, and was also seen with Astelin Nasal Spray. Local nasal mucosal irritation manifesting as epistaxis and ulceration is common with nasal spray formulation, and was also seen with Astelin.

c. Post-marketing Risk Management Activities

There are no specific safety concerns and no specific risk management activities are warranted.

d. Post-marketing Study Commitments

There will be no post-marketing study commitments.

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/s/

Badrul Chowdhury
10/15/2008 12:43:46 PM
MEDICAL OFFICER

SUMMARY REVIEW OF REGULATORY ACTION

Date:	May 30, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-203
Applicant Name:	MEDA Pharmaceuticals
Date of Submission:	July 20, 2007
PDUFA Goal Date:	May 30, 2008
Proprietary Name:	[redacted] Nasal Spray
Established Name:	Azelastine hydrochloride
Dosage form:	Nasal Spray
Strength:	137 mcg in each 0.137 mL spray
Proposed Indications:	Treatment of symptoms of seasonal allergic rhinitis and vasomotor rhinitis
Action:	Not Approval

b(4)

1. Introduction

MEDA Pharmaceuticals submitted this 505(b)(1) application for use of a sweetened nasal spray formulation of azelastine hydrochloride (called [redacted] in this review) for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 5 years of age and older and for treatment of symptoms of vasomotor rhinitis (VMR) in patients 12 years of age and older. The proposed dose is 1 or 2 sprays per nostril twice daily for SAR in patients 12 years of age and older, 1 spray per nostril twice daily for SAR in patients 5 to 11 years of age, and 2 sprays per nostril twice daily for VMR in patients 12 years of age and older. The applicant wishes to market this sweetened formulation of azelastine nasal spray because the currently marketed formulation, Astelin Nasal Spray, has a high frequency of reports of a distinctive bitter taste that has apparently limited patient acceptance. The bitter taste is from the drug substance azelastine hydrochloride. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on clinical efficacy and safety studies.

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2. Background

Azelastine is an antagonist of the histamine H1 receptor. Antihistamines are used for symptomatic treatment of various allergic diseases, such as allergic rhinitis, allergic conjunctivitis, and urticaria. The applicant has an ophthalmic formulation of azelastine marketed in the United States under the trade name Optivar, and a nasal spray formulation of azelastine marketed in the United States under the trade name Astelin. Astelin was approved in November 1996 for SAR, and in September 2000 for VMR.

The indications and dosage and administration recommendations for various ages of Astelin are identical to those proposed for / [redacted] in the current application.

There are many drugs approved for use in patients with allergic rhinitis, most of them belonging to classes of H1 receptor antagonists, nasal corticosteroids, and the leukotriene receptor antagonist montelukast. The numbers of drugs approved for non-allergic rhinitis are limited. Flonase (fluticasone propionate) Nasal Spray has a label indication of nonallergic rhinitis, and Astelin (azelastine hydrochloride) has a label indication of VMR. No other drug has a specific VMR indication. b(4)

The applicant proposed development of [redacted] using a comparability approach referring to the Agency Draft Guidance on Allergic Rhinitis.[1] This Draft Guidance mentions general paths for supporting approval of changes in formulation using a comparability approach. The guidance does not define how comparability can be established, and also there is no prior precedence of accepting comparability as the basis of approval for a nasal spray product. In a meeting with the applicant held on May 3, 2005, the Division agreed that a comparability approach based on a single clinical study may support approval of [redacted] for SAR in patients 5 years of age and older and also for VMR. The Agency stated in the meeting that "demonstration of clinical comparability should be convincing" and "whether clinical comparability is demonstrated will be a review issue." The single clinical study was the subject of a Special Protocol Assessment (SPA). On review of the SPA the Division agreed to the general concept of the study design. In the SPA letter (dated November 4, 2005) the Agency stated that a "separate clinical safety program to support the safety of the reformulated product" will be needed. These points are relevant to the action of the application. The applicant's position is that the single clinical study conducted in patients 12 years of age and older in SAR patients has shown comparability between Astelin and [redacted] and should be sufficient for approval of the SAR indication in patients 5 years of age and older, and also the VMR indication for patients 12 years of older. The Division has a different conclusion and view as discussed further in section 7c of this review. b(4)

Of note, the applicant has partnered with [redacted] The applicant proposes to [redacted]

3. Chemistry, Manufacturing, and Controls

The drug substance azelastine hydrochloride is a well known compound that is already approved in commercial ophthalmic and nasal spray products as mentioned above. [redacted] is a 0.1% w/v solution of azelastine hydrochloride adjusted to a target pH of 6.4. The major difference between the currently marketed Astelin and the proposed [redacted] is that the latter contains two additional excipients, sucralose at [redacted] w/v and b(4)

[1] Guidance for Industry. Allergic Rhinitis: Clinical Development Program for Drug Products. Draft Guidance. Available at www.fda.gov/cder/guidance.

sorbitol at [redacted] w/v. These two excipients are added to give the formulation a sweet taste with the intent that the sweet taste will mask the distinctive bitter taste of azelastine. Sucralose is a novel excipient for a nasal spray. Sorbitol has been used in other nasal sprays, but at concentrations much lower than the concentration in [redacted] The drug substance source, manufacturing, and specifications are the same for Astelin and [redacted] Both products deliver 137 mcg azelastine hydrochloride per 0.137 mL actuation. The container and pump closure system used in [redacted] is the same as in Astelin, and the spray characteristics of the two are similar. The drug product specifications of the two are also similar. All manufacturing and testing facilities associated with this application have acceptable EER status. The submitted stability data indicate that [redacted] can be stored at room temperature with an expiry of 24 months. b(4)

4. Nonclinical Pharmacology and Toxicology

A full toxicology assessment was submitted previously and reviewed under NDA 20-144 for Astelin. To support the two additional excipients the applicant submitted results from a 2-week intranasal toxicology study in dogs and a 6-month intranasal toxicology study in rats, comparing the effects of Astelin and [redacted]. The submitted studies showed that both formulations have similar toxicity profiles in the nasal mucosa and the respiratory system. Both formulations cause slight irritation of the nasal mucosa, but the magnitudes of the effects are similar. There are no outstanding nonclinical pharmacology and toxicology issues. b(4)

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic considerations for azelastine hydrochloride were addressed in the original NDA for Astelin. The applicant submitted results from one clinical pharmacology study (study MP 429) to assess comparative bioavailability between Astelin and [redacted] following a single dose. The study was conducted in 18 healthy male subjects ages 18 to 50 years. The results of the study showed that there was slightly lower exposure to azelastine and the major active metabolite, desmethyazelastine, for [redacted] compared to Astelin. The mean azelastine Cmax was 200 pg/mL and 235 pg/mL for [redacted] and Astelin, respectively, and the mean azelastine AUC was 4917 pg.hr/mL and 5903 pg.hr/mL for [redacted] and Astelin, respectively. The numerical differences for desmethyazelastine for the two formulations were similar. The lower systemic exposure from [redacted] compared to Astelin is supportive of systemic safety of [redacted], meaning that the systemic safety profile for [redacted] is not expected to be worse than Astelin. b(4)

6. Clinical Microbiology

The final product is not sterile, which is acceptable for a nasal spray product. The manufacturing process is adequate from a microbiological perspective. The drug product contains benzalkonium chloride as an [redacted].

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

The clinical program submitted with this application consists of three pivotal studies. The relatively small clinical program is acceptable given that Astelin is an approved product and that the intent of the clinical program was to establish comparability of [redacted] to Astelin. Some characteristics of these pivotal clinical studies that form the basis of the regulatory decision are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

b(4)

Table 1. Pivotal clinical studies

ID	Disease *Study type*	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
MP 430	SAR *Efficacy and safety* *Comparability*	2 weeks	12-83	[redacted] 1 spray BID [redacted] 2 sprays BID A 1 spray BID A 2 sprays BID Pbo 1 spray BID Pbo 2 sprays BID	139 146 137 138 137 138	2006	USA
MP 432	Allergic rhinitis Nonallergic rhinitis *Long term safety* *Comparability*	52 weeks (6 month Interim)	12-82	[redacted] 2 sprays BID A 2 sprays BID	281 278	On-going	Australia, Europe
[redacted]							

b(4)

b(4)

* [redacted] = [redacted] Nasal Spray; A = Astelin Nasal Spray; Pbo = Placebo Nasal spray; MF = mometasone furoate nasal spray (Nasonex);
# Year study subject enrollment ended

b. Design and conduct of the studies

Study MP 430 was a randomized, double-blind, placebo-controlled, parallel-group design study conducted in patients 12 years of age and older with SAR. The study had a 7 day placebo run-in period followed by a 2 week double-blind treatment period. The primary efficacy endpoint was change from baseline in morning plus evening reflective total nasal symptoms score (rTNSS: sum of runny nose, sneezing, itchy nose, and nasal congestion; each scored on 0-3 scale) averaged over 2 weeks of treatment. Secondary efficacy variable included the instantaneous recording of the same four symptoms (iTNSS) and the Rhinoconjunctivits Quality of Life Questionnaire (RQLQ). Safety assessments included recording of adverse events, vital signs, physical examinations, and clinical laboratory measurements.

Study MP 432 was a randomized, open-label active-controlled, parallel-group design study conducted in patients 12 years of age and older with perennial allergic rhinitis and non-allergic rhinitis. The study had a 7 day screening period followed by a 52 week open label treatment period. Safety assessments included recording of adverse events, vital signs, and physical examination with a focused nasal examination. Efficacy was assessed

by the Mini RQLQ. The applicant submitted results from a 6 months interim analysis with the NDA and submitted a 4-month safety update during the NDA review period.

b(4)

c. Efficacy findings and conclusions

The submitted clinical studies, along with the known findings of Astelin, are adequate to support the efficacy of [redacted] for SAR in patients 12 years of age and older. The clinical studies do not support approval of [redacted] for SAR in patients 5 to 11 years of age, and also do not support approval of the VMR indication. The applicant contends that [redacted] should have indications and dosage and administration recommendations for various ages identical to Astelin. The applicant's contention is based on their determination that the submitted data has demonstrated comparability between [redacted] and Astelin, and therefore, all indications and dosage and recommendation for various ages should be carried over from Astelin to [redacted] The Division disagrees with the applicant's contention. In subsequent sections three areas – SAR in patients 12 years of age and older, SAR in patients 5 to 11 years of age and older, and VMR in patients 12 years of age and older – are discussed.

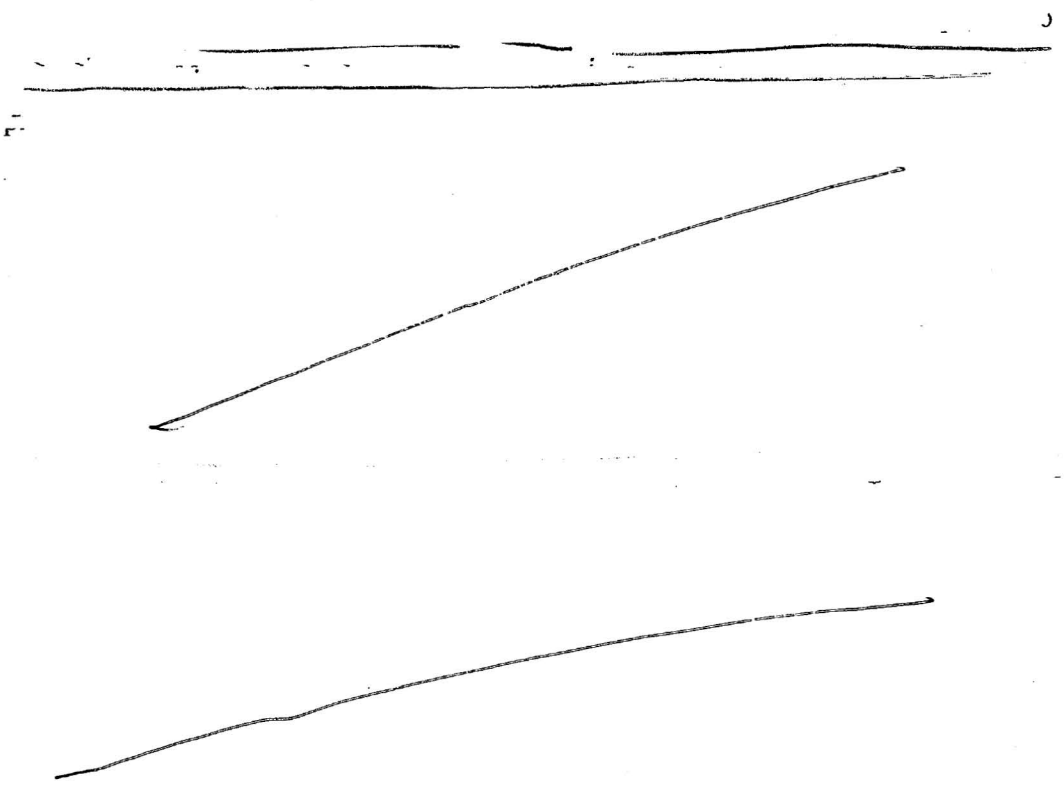
b(4)

SAR in patients 12 years of age and older, and comment on comparability

In study MP 430 the 2 spray doses of [redacted] and Astelin were both statistically significantly superior to placebo for the primary efficacy endpoint, but the 1 spray dose of both products did not statistically significantly separate from placebo (Table 2). Secondary efficacy variables generally trended in a similar direction for both products and for both doses (data not shown in this review). This single study conducted in patients with SAR ages 12 years and above is sufficient to support efficacy in SAR for ages 12 years and older. The Agency typically relies on findings from replicate studies as substantial evidence of efficacy, but in this specific instance a single study is adequate because of previous findings with Astelin, and the fact that both Astelin and [redacted] are solution formulations with similar container and closure systems and in vitro characteristics. The dosing recommendation of both 2 sprays and 1 spray can be carried over to [redacted]. Although the data from this study shows that 1 spray of both formulations did not statistically significantly separate from placebo, the efficacy trends for both 2 sprays and 1 spray favored [redacted] over Astelin (Table 2). There is no reason to believe that [redacted] at 1 spray per nostril would not be efficacious in SAR, as previous placebo controlled studies have shown a statistically significant difference between Astelin at 1 spray per nostril twice daily and placebo.

b(4)

b(4)



b(4)

Comment on Comparability:

The decision to approve the SAR indication for ages 12 years of older is based on the reasoning stated above and is not based on demonstration of comparability. For this specific decision one does not even need to conclude whether comparability of the two products has been demonstrated. Nevertheless, it is worth commenting on comparability because the applicant has concluded that comparability between [redacted] and Astelin has been demonstrated through study MP 430. b(4)

As mentioned above in section 2 of this review above, the Agency Draft Guidance on Allergic Rhinitis mentions a comparability approach to support approval of changes in formulation.[2] This Draft Agency Guidance recommends demonstration of comparability

[2] Guidance for Industry. Allergic Rhinitis: Clinical Development Program for Drug Products. Draft Guidance. Available at www.fda.gov/cder/guidance

in a single study using two doses of each formulation and demonstration of comparability of the dose-response curves. This principle was conveyed to the applicant on a meeting dated May 3, 2005. The single study MP 430 was conducted to show comparability but failed to show dose-response because the 1 spray per nostril twice daily dose, which is an approved dose for SAR, did not statistically separate from placebo (Table 2). Without demonstration of dose-response, comparability cannot be assessed. Therefore, based on this approach, the submitted study has failed to show comparability between [redacted] and Astelin. b(4)

Another approach to assess comparability of two nasal spray products is to use the principle outlined in another related Agency Guidance document.[3] This guidance is on the development of generic nasal spray products. This guidance requires that the two products be qualitatively and quantitatively the same, meaning that they both contain same active and inactive ingredients and the amount of each be within 5%. [redacted] and Astelin are qualitatively and quantitatively different because of the presence of two excipients in [redacted] that are not present in Astelin; however, because these two are solution formulationswith the same container and closure system and similar in vitro characteristics, one can assume that the differences in excipients will not impact the rate and extent of availability of the active moiety at the site of action on the nasal mucosa. Therefore, the criteria of bioequivalence described for clinical study in the guidance document are not unreasonable to apply here as a test of comparability. The design and conduct of study MP 430 are similar to the study recommended in the guidance document and allows for such analyses. Our statistical team performed equivalence analysis for [redacted] and Astelin, which shows that the two products fail the bioequivalence test (Table 3). The guidance document recommends testing at the lowest labeled dose to optimize sensitivity. In study MP 430 the lowest labeled dose, 1 spray each nostril twice daily, did not even statistically separate from placebo and should not be tested. Nevertheless, both the 1 spray and the 2 sprays doses were tested and both failed. For the 2 sprays dose, with which both Astelin and [redacted] statistically significantly separated from placebo, [redacted], tended to be numerically better than Astelin (Table 3). b(4) b(4)

It appears that adding the two excipients has changed the efficacy of azelastine. The efficacy of [redacted] may be better than Astelin in treating SAR, but the efficacy of [redacted], and Astelin is certainly not comparable.

Table 3. Equivalence analysis for the change from baseline of rTNSS* (study MP 430) b(4)

Treatment comparisons	Baseline Mean	Baseline Median
	90% CI for the ratio of means	90% CI for the ratio of means
Astelin and [redacted], 2 sprays	0.986, 1.466	0.986, 1.464
Astelin and [redacted], 1 spray	0.866, 1.324	0.867, 1.323
* To pass BE equivalence test the 90% CI must fall between 0.8 and 1.25		

[3] Guidance for Industry. Bioavailability and bioequivalence studies for nasal aerosol and nasal spray for location action. Available at www.fda.gov/cder/guidance

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Summary Review- 3

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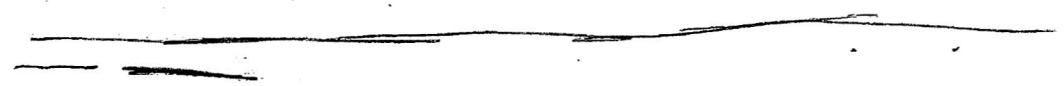

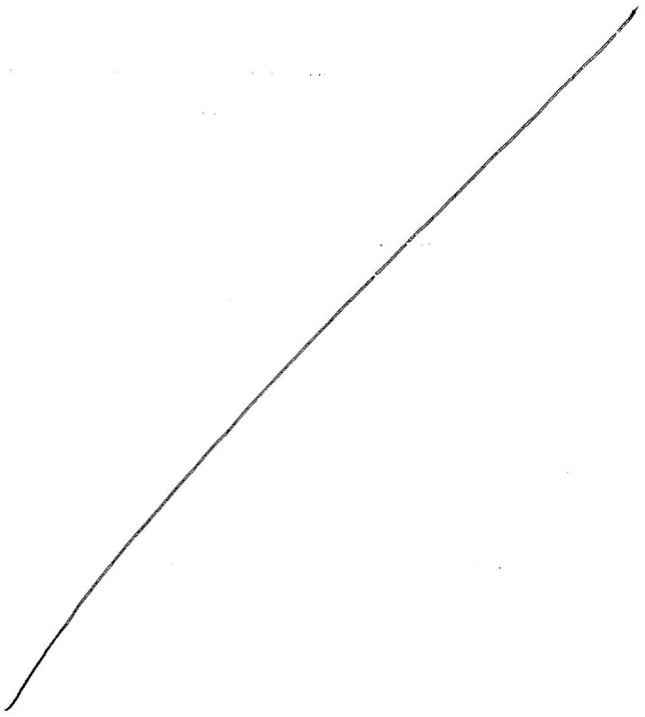

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b(4)

8. Safety

a. Safety database

The safety assessment of ——— was based on the studies MP 430 and MP 432 (Table 1). A total of 564 patients 12 years of age and older were exposed to ——— in these two studies 2 weeks and 6 months in duration. The overall safety database was adequate.

[5] Adkinson F. Middleton's Allergy. Principles and Practice, 6th ed, pg 1405.

[6] Dykewiza M, Fineman S. Executive Summary of Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis. Ann Allergy Asthma Immunol 1998; 81: 463-468

[7] Product labels for Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, and ProAir HFA Inhalation Aerosol.

b. Safety findings and conclusion

The submitted data support the safety of [redacted] 12 years of age and older. As mentioned above the application does not support safety for ages 5 to 11 years. There were no deaths in the clinical program. Serious adverse events were few and did not suggest a new safety signal. The majority of the adverse events were mild and generally similar between [redacted] and Astelin. Common adverse events that occurred more in drug treated groups compared to placebo in the 2 week study were bitter taste, epistaxis, headache, nasal discomfort, fatigue, and somnolence. In the long-term safety study reporting of adverse events was similar. Nasal mucosal ulcerations and epistaxis were seen in both active treatment arms in similar frequency. b(4)

Addition of the two sweetening agents did not seem to mask the bitter taste of azelastine. In the 2 week study, bitter taste was the commonest adverse event reported for both formulations, with a frequency of 7% and 6% with [redacted] 2 prays per nostril twice daily and 1 spray per nostril once daily, respectively, and 8% and 10% with Astelin 2 prays per nostril twice daily and 1 spray per nostril once daily respectively. This is not surprising because bitter taste receptors are in the back of the tongue whereas sweet taste receptors are mostly at the tip of the tongue. A nasal spray formulation drips to the back of the tongue and does not reach the tip of the tongue in any substantial amount. b(4)

c. REMS/RiskMAP

Not relevant because (b) (4) will not be approved in this cycle. Other antihistamines do not have REMS and RiskMAP, and, barring any new safety findings [redacted] will not require REMS or RiskMap when approved. b(4)

9. Advisory Committee Meeting

An advisory committee was not convened for this application. Azelastine is not a new molecular entity. Antihistamines, including nasal antihistamines, are a well studied drug class, and efficacy and safety of this class of drug, including azelastine, is fairly well understood. The efficacy and safety findings seen in the clinical program were fairly obvious. There were no issues that warrant discussion at an advisory committee meeting.

10. Pediatric

This NDA does not trigger PREA because there is no new active ingredient, no new indication, no new dosage form, no new dosing regimen, or no new route of administration. The applicant has a reasonable pediatric development plan for azelastine nasal spray. During approval of Astelin supplement (NDA 20-114, February 17, 2006) for 1 spray per nostril twice daily dosing for SAR, studies in children 2 years of age and older was deferred, and studies below 2 years of age was waived. The Division has taken the position that SAR does not occur in children below 2 years of age. Although the lower age cut-off is somewhat arbitrary, there is literature support for the lower age bound (J Allergy Clin Immunol 2000; 106:832). The deferred pediatric studies will adequately address all pediatric drug development for azelastine nasal spray down to the age of 2 years.

11. Other Relevant Regulatory Issues

a. DSI Audits

No DSI audit was requested for this application because azelastine nasal spray is a well studied product, and the two clinical studies conducted with [redacted] were fairly routine standard studies. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards. b(4)

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There were 3 investigators with significant equity interest in MEDA or its predecessor. The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that equity interests could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consult reviews received from DDMAC.

12. Labeling

a. Proprietary Name

The applicant proposed the trade name [redacted], for this product. DMEDP reviewed this trade name and found it unacceptable. The applicant submitted two additional trade names, [redacted] and [redacted], both of which were not acceptable to DMEDP. The problem with these trade names is that the root name for the product is the same, and the suffix contains an abbreviation that does not convey any specific meaning. Subsequently the applicant submitted two other trade names, Astepro and [redacted] DMEDP has not rendered a final decision on acceptability of these two trade names. b(4)

b. Physician Labeling

The applicant submitted a label in the Physician's Labeling Rule format that generally contains information consistent with other products of this class. The label was reviewed by various disciplines of this Division, and by DDMAC, and DMEDP. Various changes to different sections of the label were recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. The Division and the applicant have not agreed to the final version of the label because of a lack of agreement on the VMR indication and SAR indication in patients 5 to 11 years of age.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, DDMAC, and DMEP, and the last version was found to be acceptable.

d. Patient Labeling and Medication Guide

The patient instructions for use was reviewed by various disciplines of this Division, and DSRCS, and found to be acceptable.

13. Action and Risk Benefit Assessment

a. Regulatory Action

b(4)

The applicant has submitted adequate data to support approval of [redacted] for the relief of symptoms of SAR in patients 12 years of age and older. The submitted data do not support approval for SAR in patients 5 to 11 years of age, and VMR for 12 years of age and older. The action on this application will be Not Approval.

The following two comments can be used to create the action letter.

1. The data from the submitted clinical studies are not adequate to establish efficacy and safety of [redacted] for the relief of symptoms of vasomotor rhinitis for patients 12 years of age and older. [redacted]

b(4)

2. The data from the submitted clinical studies are not adequate to establish efficacy and safety of [redacted], for relief of symptoms of seasonal allergic rhinitis for patients 5 to 11 years of age.

b(4)

efficacy and safety of [redacted], for relief of symptoms of seasonal allergic rhinitis for ages 12 years and above, [redacted]

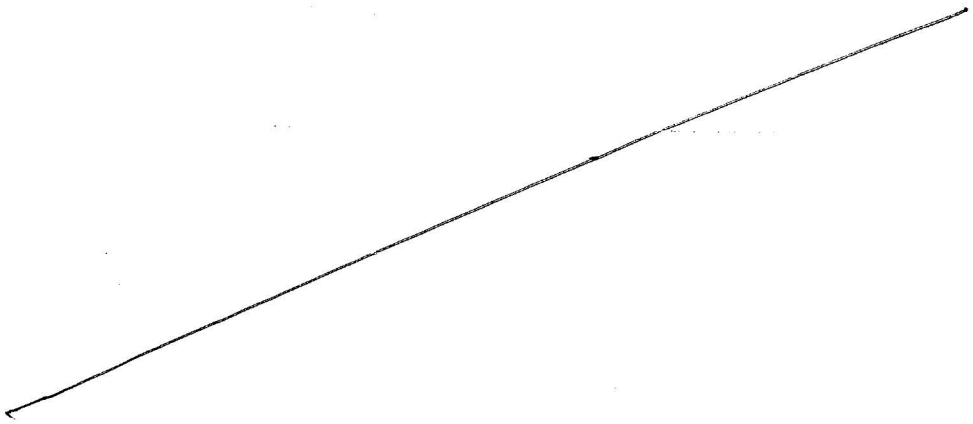
3. [redacted]

b(4)

b. Risk Benefit Assessment

The overall risk and benefit assessment of [redacted] support its approval for relief of symptoms of SAR in patients 12 years of age and older without any specific restrictions, but not for patients with SAR ages 5 to 11 years of age and not patients with VMR. The submitted clinical study showed efficacy in SAR patients ages 12 years and older, and the safety profile was acceptable for this age group. The major safety findings of clinical concern were somnolence, fatigue, epistaxis, and nasal mucosal ulcerations. Sedation manifesting as somnolence and fatigue is common with some antihistamines, and was also seen with Astelin Nasal Spray. Local nasal mucosal irritation manifesting as epistaxis and ulceration is common with nasal spray formulation, and was also seen with Astelin.

b(4)



b(4)

c. Post-marketing Risk Management Activities
Not relevant because the application will not be approved.

d. Post-marketing Study Commitments
Not relevant because the application will not be approved.

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/s/

Badrul Chowdhury
5/30/2008 11:37:58 AM
MEDICAL OFFICER
Div Dir summary review