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

* 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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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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_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

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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]

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