

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 sprays 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 Pharmaceuticals 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.

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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.

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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 **b(4)**

PDUFA Goal Date: May 30, 2008

Proprietary Name: _____ 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

1. Introduction

MEDA Pharmaceuticals submitted this 505(b)(1) application for use of a sweetened nasal spray formulation of azelastine hydrochloride (called _____ 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. **b(4)**

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 / _____ 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.

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The applicant proposed development of _____, 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 _____ 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 _____ 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.

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Of note, the applicant has partnered with _____,

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_____ the applicant proposes to

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.

_____ 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 _____ is that the latter contains two additional excipients, sucralose at _____ w/v and _____

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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.

sorbitol at _____ 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 / _____. The drug substance source, manufacturing, and specifications are the same for Astelin and _____. Both products deliver 137 mcg azelastine hydrochloride per 0.137 mL actuation. The container and pump closure system used in _____ 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 _____ can be stored at room temperature with an expiry of 24 months.

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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 _____. 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.

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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 _____ 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 _____ compared to Astelin. The mean azelastine C_{max} was 200 pg/mL and 235 pg/mL for _____ and Astelin, respectively, and the mean azelastine AUC was 4917 pg.hr/mL and 5903 pg.hr/mL for _____ and Astelin, respectively. The numerical differences for desmethyazelastine for the two formulations were similar. The lower systemic exposure from _____ compared to Astelin is supportive of systemic safety of _____, meaning that the systemic safety profile for _____ is not expected to be worse than Astelin.

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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 _____.