CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-203

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 22-203	**TRADE NAME:**	Astepro® Nasal Spray
APPLICANT/SPONSOR:	Meda Pharmaceuticals	**USAN NAME:**	Azelastine hydrochloride
MEDICAL OFFICER:	Susan Limb, MD		
TEAM LEADER:	Sally Seymour, MD	**CATEGORY:**	Antihistamine
REVIEW DATE:	October 8, 2008	**ROUTE:**	Intranasal inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
August 14, 2008	August 15, 2008	N017	Class 1 resubmission for adult SAR indication following dispute resolution

REVIEW SUMMARY: This is a medical officer review of labeling submitted for Astepro® Nasal Spray following a Not Approvable action the first cycle and subsequent dispute resolution. Astepro Nasal Spray is an antihistamine nasal spray that contains 0.1% azelastine hydrochloride with sucralose and sorbitol. Astepro is a new formulation developed by MEDA to address the bitter taste of the currently marketed azelastine nasal spray, Astelin Nasal Spray. NDA 22-203 for Astepro was first submitted on July 30, 2007, with the following proposed indications: 1) treatment of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older at 1 or 2 sprays per nostril twice daily; 2) treatment of the symptoms of SAR in patients 5 to 11 years of age at 1 spray per nostril twice daily; and 3) treatment of the symptoms of vasomotor rhinitis (VMR) in patients 12 years of age and older at 2 sprays per nostril twice daily. The proposed indications were the same as the approved indications for the original, unsweetened intranasal formulation of azelastine, Astelin® Nasal Spray.

NDA 22-203 was reviewed and a Not Approval action was taken (May 30, 2008). Details of the original clinical review can be found in the attached primary medical officer's review dated February 29, 2008. The Not Approval letter cited the following clinical deficiencies: 1) pediatric indication not supported [redacted] in patients 5 to 11 years of age; 2) [redacted] in patients with vasomotor rhinitis (VMR); and 3) [redacted] b(4)

The Applicant requested a formal dispute resolution on July 1, 2008. A dispute resolution meeting with the Applicant was held on July 28, 2008. The Applicant stated that comparability between Astepro and Astelin had been demonstrated, and on the basis of comparability, the indications and dosing recommendations approved for Astelin should also be approved for Astepro. After deliberation, Dr. Curtis Rosebraugh, Director of the Office of Drug Evaluation II, Center for Drug Evaluation and Research, supported the Applicant's request for approval of the SAR indication in patients 12 years and older. However, Dr. Rosebraugh supported DPAP's findings that the application lacked sufficient data to support the SAR indication in patients 5 to 11 years, the VMR indication in patients 12 years of age and older, and an [redacted] b(4)
A detailed discussion of the dispute resolution is found in the copy of Dr. Rosebraugh's Response to a Formal Dispute Resolution Appeal attached to this document.

In this resubmission, the Applicant submitted proposed labeling for Astepro for the SAR indication in patients 12 years of age and older, including caveats against use in patients under the age of 12 years. The VMR indication [redacted] b(4)
information have also been removed. These changes are appropriate and consistent with the deficiencies in the NA letter and decision from the Dispute Resolution. Additional minor changes suggested by the review team have been incorporated in the labeling, including clarification of the findings in the QT study (Section 12.2), minor wording and typographical edits, and updates to the carton/container label. The suggested edits can be found highlighted in the attached label. Of note, Section 6, Adverse Reactions, is based on data from a completed 2-week safety and efficacy trial and the 6-month interim report of a 1-year safety study. The Applicant has agreed to submit the final study report in January 2009 at which time this section of the label will be updated to include 12-month safety data.

Assuming acceptance of the labeling revisions and no further changes to the proposed label, the Class I resubmission is recommended for Approval.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: X **APPROVAL** **COMPLETE RESPONSE**

I. Summary

Meda submitted a 505(b)(1) new drug application (NDA# 22-203) on July 30, 2007, for a sweetened azelastine nasal spray for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 5 years of age and older and for the treatment of vasomotor rhinitis (VMR) in patients 12 years of age and older. The proposed dosing regimen is 1-2 sprays twice daily. An unsweetened azelastine nasal spray is currently approved for the same indications (NDA# 20-114, Meda) under the tradename Astelin Nasal Spray, but because of the bitter taste, Meda developed the proposed sweetened formulation, which contains the additional excipients, sucralose and sorbitol.

A Not Approval was taken on NDA# 22-203 on May 30, 2008, with the following clinical deficiencies (paraphrased): 1) pediatric indication not supported because of [redacted] in patients 5 to 11 years of age; 2) [redacted] in patients with vasomotor rhinitis (VMR); and 3) [redacted] b(4)

The clinical program conducted by MEDA was based upon a comparability approach with Astepro Nasal Spray and Astelin Nasal Spray. Details of the original clinical review can be found in the primary medical officer's review dated February 29, 2008. Of note, the original clinical review recommended an Approval action for the SAR indication in patients 12 years of age and older on the basis of the safety and efficacy demonstrated in the pivotal study and the previous studies for Astelin Nasal Spray. A Not Approval action was recommended for the SAR indication in patients 5 to 11 years of age and the VMR indication. The original review also concluded that an [redacted] for SAR was not supported. These recommendations were made at the time of the review in anticipation of an administrative decision to split the proposed indications and on the presumption that agreement would be made on labeling. However, at the time of the action, no agreement on labeling had been reached and a Not Approval letter was issued as outlined above. The Not Approval action recommended by the larger clinical team was consistent with the primary medical officer's recommendations. In addition, the primary medical officer's review came to the conclusion that Astepro and Astelin were comparable, whereas subsequent clinical reviews have concluded that comparability was not demonstrated. Comparability is not a clearly defined concept as applied to nasal spray products. The original assessment of comparability made in the initial clinical review was not based on a formal definition of comparability, such as the definition presented in the Draft Guidance on Allergic Rhinitis, April 2000, or the Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003. When criteria from either of these guidances are applied to the Astepro data, comparability between Astepro and Astelin is not demonstrated. b(4)

The Applicant requested a formal dispute resolution on July 1, 2008. A dispute resolution meeting with the Applicant was held on July 28, 2008. The Applicant stated that comparability between Astepro and Astelin had been demonstrated, and on the basis of

comparability, the indications and dosing recommendations approved for Astelin should also be approved for Astepro. After deliberation, Dr. Curtis Rosebraugh, Director of the Office of Drug Evaluation II, Center for Drug Evaluation and Research, supported the Applicant's request for approval of the SAR indication in patients 12 years and older. However, Dr. Rosebraugh supported DPAP's findings that the application lacked sufficient data to support the SAR indication in patients 5 to 11 years, the VMR indication in patients 12 years of age and older, and ———————— . A detailed discussion of the dispute resolution is found in the copy of Dr. Rosebraugh's Response to a Formal Dispute Resolution Appeal attached to this document. b(4)

In this resubmission, the Applicant submitted proposed labeling for Astepro for the SAR indication in patients 12 years of age and older, including caveats against use in patients under the age of 12 years. The VMR indication and ———————— information have also been removed. These changes are appropriate and consistent with the deficiencies in the NA letter and decision from the Dispute Resolution. Additional minor changes suggested by the review team have been incorporated in the labeling, including clarification of the findings in the QT study (Section 12.2), minor wording and typographical edits, and updates to the carton/container label. The suggested edits can be found highlighted in the attached label. Of note, in Section 6, Adverse Reactions, is based on data from a completed 2-week safety and efficacy trial and the 6-month interim report of a 1-year safety study. The Applicant has agreed to submit the final study report in January 2009 at which time this section of the label will be updated to include 12-month safety data. b(4)

II. Attachments

1. Proposed labeling for Astepro Nasal Spray
2. Dr. Susan Limb's Medical Officer Review of NDA# 22-203, dated February 29, 2008
3. Response to Request for Formal Dispute Resolution, dated August 7, 2008

16 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓
_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-203
Submission Code	N000
Letter Date	July 30, 2007
Stamp Date	July 30, 2007
PDUFA Goal Date	May 30, 2008
Reviewer Name	Susan Limb, MD
Review Completion Date	February 29, 2008
Established Name	Azelastine hydrochloride (sweetened)
(Proposed) Trade Name	[redacted] b(4)
Therapeutic Class	Intranasal antihistamine
Applicant	Medpointe Pharmaceuticals
Priority Designation	S
Formulation	Intranasal solution
Dosing Regimen	1 or 2 sprays each nostril BID
Indication	Seasonal allergic rhinitis
Intended Population	Patients 5 years of age and older

Table of Contents