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Summary

In summary, I appreciate that you and the Division have worked to try to reconcile your differences in approach to this application, even though you have been unsuccessful. I agree with you that this product can be approved for marketing for the SAR indication for ages 12 years and above, with the caveat that labeling would have to omit references to — and VMR until you submit data that would allow these claims. However, I agree with DPAP that further safety data are required for those under 12 years of age and further studies are needed for the OOA and VMR claims.

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The approach that I suggest, approval for SAR for 12 and above, will allow marketing of your new product while you work towards obtaining the full labeling that your current product enjoys. This is consistent with our approach to the CFC to HFA propellant switch for albuterol. I recommend you consult with the Division as to the type and design of studies needed to supply the requisite data to reconcile the identified deficiencies.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. This appeal should be sent again through the Center's Dispute Resolution Project Manager, Ms. Kim Colangelo, at the following address:

Ms. Kim Colangelo  
Dispute Resolution Project Manager  
Office of New Drugs  
FDA, Bldg 22, Room 6460  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

A copy should also be submitted to the NDA at the usual address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anesthesia, Analgesia, and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions concerning this response, contact Ms. Lee Ripper at (301) 796-1282.  
If you have any questions concerning an appeal to Dr. Jenkins, contact Ms. Colangelo at (301) 796-0140.

Sincerely,

*{See appended electronic signature page}*

Curtis Rosebraugh, M.D., M.P.H.  
Director  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

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Curtis Rosebraugh  
8/7/2008 02:48:46 PM

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/s/

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Susan L Limb  
10/15/2008 11:54:12 AM  
MEDICAL OFFICER

Sally Seymour  
10/15/2008 12:16:22 PM  
MEDICAL OFFICER  
I concur.

**MEDICAL OFFICER REVIEW**  
**Division of Pulmonary and Allergy Products**

<b>Application #:</b> NDA 22-203	<b>Application Type:</b> NDA
<b>Sponsor:</b> Medpointe Pharmaceuticals	<b>Proprietary Name:</b> _____
<b>Investigator:</b>	<b>USAN Name:</b> Azelastine hydrochloride
<b>Category:</b> Antihistamine	<b>Route of Administration:</b> Intranasal inhalation
<b>Reviewer:</b> Susan Limb, MD	<b>Review Date:</b> September 6, 2007

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**SUBMISSIONS REVIEWED IN THIS DOCUMENT**

<b>Document Date</b>	<b>Submission Type</b>	<b>Comments</b>
July 30, 2007	NDA 22-203	Paper and electronic submission

**REVIEW SUMMARY:** This is a 45-day filing and planning review of a 505(b)(1) NDA for sweetened intranasal azelastine. The original unsweetened formulation (Astelin, 137 mcg) was first approved on November 1, 1996 (NDA 20-114) for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 5 years of age and older and for treatment of the symptoms of vasomotor rhinitis (VMR) in patients 12 years of age and older. The active drug substance, azelastine hydrochloride, has a bitter taste and users report dysgeusia as the most common adverse event. The Applicant has reformulated the drug product to contain sucralose as a taste-masking agent. The sweetened formulation is intended for the same indications and dosage as Astelin. Of note, the Applicant plans to \_\_\_\_\_

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In addition to preclinical and clinical data previously reviewed in NDA 20-114, the Applicant has provided the results of toxicology studies using the sweetened formulation, CMC information, and three new clinical studies to demonstrate comparability and safety, as \_\_\_\_\_  
\_\_\_\_\_ MP429 is a pharmacokinetic study; MP430 is a 2-week, 6-arm, randomized, placebo-controlled SAR trial in 835 patients; and MP-432 is a 6-month, open-label safety study. These study reports are appropriately indexed and organized to allow review. The Applicant has provided copies of proposed labeling and appropriate case report forms.

The submission is adequate to allow clinical review and is fileable.

**OUTSTANDING ISSUES:** None

**RECOMMENDED REGULATORY ACTION:**

NDA, Efficacy/Label supplement:     Fileable                       Not fileable

**Medical Reviewer:** Susan Limb, MD

**Medical Team Leader:** Sally Seymour, MD

## I. General Information

Astelin (azelastine) is a selective, H1 antihistamine administered as an intranasal spray. Astelin is currently approved for the following indications:

- Seasonal allergic rhinitis (SAR)
  - Children 5 to 11 years, 1 spray per nostril twice daily
  - Adults and children 12 years of age and older, 1 or 2 sprays per nostril twice daily
- Vasomotor rhinitis (VMR) in adults and children 12 years of age and older, 2 sprays per nostril twice daily

Due to a distinctive bitter taste that limits marketing of Astelin and patient compliance, Medpointe Pharmaceuticals has developed a sweetened intranasal azelastine formulation, MP03-33, containing sucralose as a taste-masking agent. The proposed tradename for MP03-33 is (b) (4). The proposed indications and dosages for MP03-33 are the same as those carried by the reference product, Astelin. The following table compares the components of MP03-33 and Astelin.

Component	MP03-33 (% w/v)	Astelin (% w/v)	Function
Azelastine hydrochloride	0.100	0.100	Active ingredient
Hypromellose, USP			
Edetate disodium, USP			
Benzalkonium chloride, ND			
Citric acid, USP			
Dibasic sodium phosphate, USP			
Sodium chloride, USP			
Sodium citrate, USP			
Sucralose, NF			
Sorbitol, USP			
Purified water, USP			

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The proposed drug product contains 0.1% w/v azelastine hydrochloride and is packaged as a 30mL fill volume in \_\_\_\_\_ mL high density polyethylene bottles (HDPE) fitted with a metered spray pump for trade and a \_\_\_\_\_ mL fill volume in \_\_\_\_\_ bottles for sample and trade.

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The 505(b)(1) application is a paper and electronic submission.

## II. Clinical development program

The Applicant's drug development program relies on the Agency's previous findings of efficacy and safety of the approved reference product, Astelin, in addition to toxicology data on MP03-33, pharmacokinetic comparisons between MP03-33 and Astelin, a 2-week SAR efficacy study, a 6-month safety study, \_\_\_\_\_ . These studies are described in more detail in a later section of this review.

The table below outlines the clinical studies included in the application.

Study	Subjects	Design	Dose	Duration	Relevance
MP429*	54 healthy adult males	R, open-label, parallel group, single-dose	1 or 2 sprays per nostril <ul style="list-style-type: none"> <li>• MP03-33</li> <li>• Astelin</li> <li>• MP03-36 (1.5% azelastine, 1.5% sucralose)</li> </ul>	Single dose	PK comparison
MP430*	1109	MC, R, DB, PC, 6-arm study	1 or 2 sprays per nostril: <ul style="list-style-type: none"> <li>• MP03-33</li> <li>• Astelin</li> <li>• Placebo</li> </ul>	2 weeks	Pivotal SAR efficacy/comparability study
MP432*	559	MC, open-label, active control	2 sprays per nostril: <ul style="list-style-type: none"> <li>• MP03-33</li> <li>• Placebo</li> </ul>	6 months	Long-term safety study

\* Primary studies to establish comparability between Astelin and MP03-33

Reviewer's Comment: A higher strength  $\frac{1}{2}$  formulation is also under development.

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### III. Foreign marketing and regulatory history

Azelastine hydrochloride nasal spray (137 mcg) is approved and marketed for the treatment of symptoms of allergic rhinitis in more than 80 countries worldwide. The Applicant reports no marketing authorization withdrawals, suspensions, failures to obtain marketing authorization renewal, restrictions on distribution or clinical trial suspensions (Vol 1, Page 216).

- November 1, 1996 - Astelin Nasal Spray approved (NDA 20-114)
- May 3, 2005, meeting
  - Sweetened formulation proposed
  - Comparability approach is acceptable if dose response curves are comparable for two doses of old and new formulation (5 treatment arms).
  - Study statistically powered to compare active treatment arms vs. placebo is acceptable. A numeric comparison of the two different formulations will be performed.
  - For PK program, evaluate BA of new formulation and determine 90% CI of pertinent PK parameters between the new and old formulations. PK information is supportive of safety.
  - 6 month IN toxicology study with sweetened formulation required
  - Pediatric discussion deferred
- June 8, 2005, meeting
  - Clarification of toxicology requirements for sweetened formulation
- September 20, 2005, Special Protocol Assessment