

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is Approval. The application contains adequate evidence of efficacy to support the proposed indication for \_\_\_\_\_ : “the treatment of the symptoms of seasonal allergic rhinitis (SAR) in adults and adolescents 12 years of age and older.”

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This is a 505(b)(1) application for a sweetened formulation of azelastine hydrochloride nasal spray (MP03-33). The sweetened formulation contains two novel excipients, sucralose and sorbitol. An unsweetened formulation (Astelin®, NDA 20-114) was first approved for the same indication in adults and adolescents 12 years of age and older at 2 sprays twice daily on November 1, 1996; a 1-spray twice daily dose for patients 5 years of age and older was subsequently approved in a supplement to the original NDA (Supplement 014, approved February 17, 2006). In addition to preclinical and clinical data previously reviewed in NDA 20-114, the Applicant provided the results of animal toxicology studies using the sweetened formulation, supporting CMC information, and new clinical data. The clinical development program includes new clinical studies to demonstrate comparability and safety between the sweetened and unsweetened formulations, including a 2 week efficacy and safety study in patients with SAR (MP430) and a 6-month safety study (MP432).

The clinical recommendation for an Approval action is based on the submitted clinical data, as well as the established efficacy and safety of the unsweetened formulation. Study MP430, the primary efficacy trial, showed a statistically significant benefit for MP03-33 over placebo at the 2 sprays twice daily dose for the treatment of SAR symptoms. The study did not show a statistically significant benefit over placebo for the 1 spray twice daily dose; however, MP03-33 performed comparably to the approved formulation, Astelin, which was included in the trial as an active comparator. Based on these results and the Agency’s previous findings of efficacy for Astelin, the clinical review concludes that the application provides sufficient evidence to support the full range of doses for the SAR indication.

The safety of MP03-33 in SAR patients 12 years of age and older is supported by the submitted clinical study data for MP03-33 as well as the safety database to support approval of Astelin, postmarketing data and published studies on Astelin. Review of the safety data showed that MP03-33 is most commonly associated with dysgeusia, epistaxis, headache, nasal discomfort, fatigue, and somnolence, similar to the safety profile for Astelin. These adverse events are described in the current Astelin product label. No new safety signals were identified for the sweetened azelastine formulation. However, the submission did not include any safety data on MP03-33 in children ages 5 to 11 years of age.

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In summary, the application provides adequate support for the SAR indication (1 or 2 sprays twice daily) in patients 12 years of age and older for the sweetened azelastine formulation, MP03-33. \_\_\_\_\_

\_\_\_\_\_ the clinical recommendation is that the SAR indication in this lower age group remains exclusive to the currently marketed unsweetened formulation, Astelin. Likewise, \_\_\_\_\_

\_\_\_\_\_ the clinical recommendation is that the VMR indication also remains exclusive to Astelin.

### 1.2 Risk Benefit Assessment

A risk-benefit assessment for intranasal azelastine in the treatment of SAR symptoms has been previously performed in the review of the original Astelin NDA, NDA 20-114, and the subsequent supplement for the 1-spray dose (Supplement 014, approved February 17, 2006). As the efficacy and safety profile for MP03-33 appear comparable in patients 12 years of age and older to the approved product on the market, Astelin, the risk-benefit assessment remains unchanged. The application contains adequate evidence of efficacy for the proposed SAR indication with an acceptable safety profile in patients 12 years of age and older. \_\_\_\_\_

\_\_\_\_\_ the SAR indication in this age group is not recommended for approval. \_\_\_\_\_

\_\_\_\_\_ the VMR indication in all age groups is not recommended for approval.

### 1.3 Recommendations for Postmarketing Risk Management Activities

No recommendations for postmarketing risk management activities are made.

### 1.4 Recommendations for other Post Marketing Study Commitments

The recommendation for approval is for MP03-33 for patients 12 years of age and older. Astelin is currently approved in patients down to the age of 5 years. As allergic rhinitis may exist in

children <math>\geq</math> years of age, the Applicant

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No new post-marketing study commitments are recommended at this time.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Azelastine is a selective, H1 antihistamine administered as an intranasal spray. It is currently marketed under the trade name, Astelin (azelastine hydrochloride 137 mcg nasal spray), and is 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 and sorbitol as additional excipients. The proposed trade name for MP03-33 is                     . 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.

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

Source: Volume 1, Item 3, Table 3.1-2

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The proposed drug product contains 0.1% w/v azelastine hydrochloride and is packaged as a 30mL fill volume in 30 mL high density polyethylene bottles (HDPE) fitted with a metered spray pump for trade and a 4mL fill volume in 4 mL bottles for sample and trade.

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## 2.2 Tables of Currently Available Treatments for Proposed Indications

Aside from unsweetened azelastine, there are currently no other intranasal antihistamine products available for treatment of allergic rhinitis. Six long-acting oral antihistamines are currently available for the proposed product indication. A summary of these antihistamines is provided in Table 2.

Table 2 Available antihistamine treatments for allergic rhinitis			
Drug	Indications*	Dose	Age range
Desloratadine (Clarinetx®)	SAR, PAR, CIU	1 to 5 mg once daily	6 months and older
Fexofenadine (Allegra®)	SAR, CIU	30 mg to 60 mg twice daily or 180 mg once daily	6 years and older
Levocetirizine (Xyzal®)	SAR, PAR, CIU	2.5 to 5 mg once daily	6 years and older
Cetirizine (Zyrtec®)†	Allergic rhinitis, chronic hives/CIU	2.5 to 10 mg once daily	2 years of age and older (OTC); 6 months and older (Rx only)
Loratadine (Claritin®)‡	Allergic rhinitis, chronic hives	5 to 10 mg once daily	2 years of age and older (OTC)

\* SAR = seasonal allergic rhinitis; PAR = perennial allergic rhinitis; CIU = chronic idiopathic urticaria

† Available OTC for nasal allergy symptoms and hives indication; remains prescription-only for PAR in children under the age of 2 years and CIU in children under the age of 6 years

‡ Available OTC for nasal allergy symptoms and hives

## 2.3 Availability of Proposed Active Ingredient in the United States

Azelastine is currently marketed as a 0.1% intranasal spray for the treatment of the symptoms of SAR and VMR (Astelin®, NDA 20-114, approved November 1, 2006) and as 0.05% ophthalmic drops (Optivar®, NDA 21-127, approved May 20, 2000) for the treatment of itching of the eye associated with allergic conjunctivitis. No major safety concerns have been identified post-approval for either azelastine product.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Somnolence and fatigue are the most common adverse events associated with antihistamines in general, and product labels typically recommend caution when performing activities requiring mental alertness, such as driving and operating heavy machinery. Somnolence has been noted in the clinical program for both the unsweetened and sweetened azelastine nasal spray. The current Astelin label contains precaution language regarding activities requiring mental alertness. Similar language will be incorporated into the sweetened azelastine formulation label.

Terfenadine, one of the first second-generation antihistamines approved for the treatment of allergic rhinitis, was subsequently associated with QT interval prolongation and cardiac arrhythmias, leading to its removal from the market. A study evaluating the effect of intranasal



## 2.6 Other Relevant Background Information

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 (Volume 1, Page 216).

In addition, the Applicant in conjunction with [REDACTED]

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In the submission Summary, the Applicant stated the intention to [REDACTED] Astelin and [REDACTED] MP03-33.

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## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The submission included complete study reports of the three major clinical studies (MP429, MP430, MP432), proposed labeling, and appropriate case report forms. The study reports were appropriately indexed and organized to allow review. The submission included raw datasets for the three major clinical studies. [REDACTED]

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Review of the application did not raise any data integrity concerns. There were [REDACTED] investigators with financial interests/arrangements [REDACTED]; however, none of these investigators enrolled a significant number of subjects (each enrolled [REDACTED] patients). In addition, azelastine is a known drug substance with extensive post-marketing experience. Because of these reasons, no DSI review was recommended.

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### 3.2 Compliance with Good Clinical Practices

The Applicant has certified that the studies were conducted in accordance with acceptable ethical standards. Study reports indicated that informed consent was obtained from all study participants. Analysis by treatment site did not indicate any systematic site-based bias.

### 3.3 Financial Disclosures

The Applicant provided financial disclosure information for  $\nu$  investigators from Study MP430 with potential financial conflicts of interest (\_\_\_\_\_).

\_\_\_\_\_ The Applicant has certified that no disclosable financial arrangements occurred for Studies MP429, MP432, or \_\_\_\_\_, and that a diligent effort was made to obtain financial disclosure information for Study \_\_\_\_\_ which was conducted by a third party (\_\_\_\_\_).

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## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Table 1 display the ingredients in the sweetened azelastine formulation; the addition of sucralose and sorbitol are noteworthy. The proposed drug product contains 0.1% w/v azelastine hydrochloride and is packaged as a 30mL fill volume in  $\nu$  mL high density polyethylene bottles (HDPE) fitted with a metered spray pump for trade and a 4mL fill volume in \_\_\_\_\_ bottles for sample and trade. The CMC review remains pending at this time. Upon preliminary review, no major issues have been identified. The CMC reviewer has noted that the in vitro characteristics of the sweetened formulation are unchanged from the characteristics of the original unsweetened formulation despite the addition of sucralose and sorbitol.

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### 4.2 Clinical Microbiology

MP03-33 contains benzalkonium chloride as an \_\_\_\_\_ . The Applicant submitted data showing that at a concentration of  $\nu$  % the formulation amount, the effectiveness of benzalkonium chloride met the requirements of USP 29 <51>.

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### 4.3 Preclinical Pharmacology/Toxicology

The Preclinical Pharmacology/Toxicology review recommends Approval of the application. MP03-33 contains two excipients which are not present in Astelin, sucralose and sorbitol. Also, sucralose is a novel excipient for the intranasal route of administration, and the sorbitol concentration in MP03-33 is higher than that found in other approved drug products. To support the safety of these excipients, the Applicant submitted results for three 2-week intranasal irritation studies in rats and Beagle dogs and a 6-month study in rats to evaluate the safety of the sweetened azelastine formulation. Per the preclinical review, these studies demonstrated that MP03-33 and Astelin have similar toxicity profiles. Slight local irritation of the nasal cavity was the chief finding in animals. The presence of these two excipients did not enhance the effect of azelastine on the respiratory system.

Additional preclinical data to support the safety of azelastine for intranasal administration was previously reviewed under NDA 20-114. No new data on genetic toxicity, carcinogenicity, reproductive and developmental toxicity were submitted with this application.

#### **4.4 Clinical Pharmacology**

The Clinical Pharmacology review remains pending at this time. Upon preliminary review, no major issues have been identified.

##### **4.4.1 Mechanism of Action**

Azelastine is a selective H1-receptor blocker. The nasal spray is a racemic mixture. No differences in pharmacological activity have been reported between the enantiomers in in vitro studies.

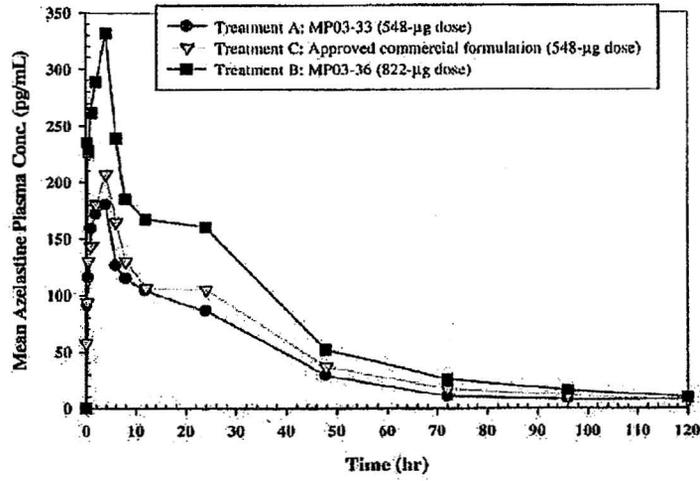
##### **4.4.2 Pharmacodynamics**

No new pharmacodynamic data is included in this submission. Pharmacodynamic data in the current product label for unsweetened azelastine states that there was no evidence of a QTc interval prolongation effect in a placebo-controlled study of azelastine 2 sprays twice daily for 56 days in patients with SAR. No formal thorough QT study has been performed for azelastine. Previous drug-drug interaction studies did not show any interactions between oral azelastine and erythromycin. Ketoconazole interfered with measurement of azelastine plasma levels but no effects on QTc intervals were observed.

##### **4.4.3 Pharmacokinetics**

The Applicant conducted Study MP429, a randomized open-label, parallel group, single-dose study in 54 healthy adult male volunteers to establish the comparability between MP03-33 and unsweetened azelastine. Subjects received 1 or 2 sprays per nostril of MP03-33, unsweetened azelastine, and MP03-36 (a different sweetened formulation containing 0.15% azelastine and 0.15% sucralose). Overall, similar systemic exposures and peak concentrations were observed for MP03-33 and Astelin for both azelastine (Figure 1) and the major active metabolite, desmethylazelastine. Dose-proportional pharmacokinetics were observed for MP03-36. A detailed review of Study MP429 can be found in the Clinical Pharmacology team's review.

**Figure 1 Study MP429: Pharmacokinetics of sweetened versus unsweetened azelastine**



*Reviewer's comment: Based on Study MP429, the pharmacokinetics of MP03-33 appear comparable to the PK parameters for the commercially available intranasal azelastine spray.*