

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-203

PHARMACOLOGY REVIEW(S)

Supervisory Pharmacologist Review

NDA: 22-203 – Astelin sweetened formulation (azelastine)
FROM: Timothy J. McGovern, Ph. D., Supervisory Pharmacologist
DATE: April 18, 2008

I concur with the recommendation by Dr. Luqi Pei, the pharmacology/toxicology reviewer, that the pharmacology and toxicology of the new sweetened intranasal formulation of azelastine has been adequately evaluated and that the drug product is approvable from a nonclinical standpoint (see Dr. Pei's original NDA review dated March 27, 2008).

The proposed intranasal drug product is similar to the previously approved Astelin product (NDA 20-114) except for the inclusion of the excipients sucralose and sorbitol. The ingredients were included in an effort to mask a perceived bitter taste of the approved formulation. The proposed azelastine dose and concentration are identical to the approved Astelin. In communications with the sponsor during product development, an acceptable nonclinical development program was agreed to regarding the adequate safety evaluation of the new formulation and the novel use of two formulation excipients sorbitol and sucralose. This program included intranasal toxicity studies of the sweetened formulation of up to 6 months in rats and dogs.

General toxicology: No new, significant toxicology data were provided to further characterize the toxicity profile of azelastine. The proposed clinical dose and azelastine concentration are identical to the approved Astelin formulation and the sponsor is referencing the previously conducted toxicology studies from NDA 20-114. This approach was considered acceptable by the Division. The current nonclinical program focused on the safety evaluation of the novel use of two excipients, sorbitol and sucralose. Sucralose is a novel excipient for intranasal use while the proposed use of sorbitol exceeds the previous use in an intranasal product. MedPointe, in agreement with the Division, conducted a bridging toxicology program that included intranasal toxicity studies of the sweetened Astelin formulation up to 6 months in rats and 2 weeks in dogs to support the reformulation. These studies included comparisons with the approved Astelin formulation. In all, the studies showed that the new sweetened Astelin formulation and the approved Astelin Nasal Spray possess similar toxicity profiles and that there is no nonclinical safety concern about the novel excipients in the new sweetened Astelin formulation.

Overall, the toxicology program supports the proposed clinical use of the drug product.

Reproductive toxicity: New studies were not conducted for this application. Azelastine is considered a Pregnancy Category C drug due to the observance of embryo-fetal death, malformations (cleft palate, short or absent tail, and fused, absent or branched ribs), delayed ossification and decreased fetal weight at maternally toxic doses in mice, malformations (oligo- and brachydactyilia), delayed ossification and skeletal variations, embryo-fetal death and decreased fetal weight in rats, and abortion, delayed ossification

and decreased fetal weight at doses that resulted in severe maternal toxicity in rabbits. Based on these findings, the sweetened formulation of azelastine should also be considered a Pregnancy Category C drug.

Genotoxicity: New studies were not conducted for this application. A previously conducted battery of studies produced negative findings.

Carcinogenicity: New studies were not conducted for this application. Studies were previously conducted in rats and mice and showed no evidence of carcinogenicity.

Labeling: In comparison with the approved Astelin label, the sweetened Astelin label was formatted according to the PLR format. The nonclinical sections of the product label were adopted from the label of the approved Astelin. All nonclinical studies pertinent to the labeling of azelastine were submitted and reviewed previously under the approved Astelin application. The current application contained no new studies of genetic toxicity, carcinogenicity, reproductive and developmental toxicity of azelastine. The sponsor edited the Pregnancy section to place text regarding the _____ use of sweetened Astelin Nasal Spray during pregnancy at the beginning of the section. In evaluating the proposed label, Dr. Pei recommended edits to the Pregnancy section to conform to recent recommendations from CDER's SEALD team to focus the text on the primary reproductive findings and the animal to human exposure ratios at which they occur. Additional details, such as the actual doses administered, are presented in Section 13.2: Animal Toxicology and/or Pharmacology - Reproductive Toxicology Studies. The recommended edits were forwarded to the sponsor and were accepted.

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In conclusion, the Division and the sponsor agreed to a bridging toxicology program to characterize the safety of the new sweetened azelastine formulation. Studies up to 6 months duration demonstrated that the new formulation was comparable to the previously approved azelastine formulation and did not reveal any significant findings of concern that would preclude approval of the drug product. Therefore, this application is considered approvable from a nonclinical perspective.

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/s/

Timothy McGovern
4/18/2008 02:29:50 PM
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-203
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 30/7/07
PRODUCT: (Azelastine HCl Nasal Spray)
INTENDED CLINICAL POPULATION: Patients with Seasonal Allergic Rhinitis (age 5 and above) or Vasomotor Rhinitis (age 12 and above)
SPONSOR: MedPointe Pharmaceuticals
DOCUMENTS REVIEWED: Vol. 1, 8 - 14
REVIEW DIVISION: Division of Pulmonary and Allergy Products
PHARM/TOX REVIEWER: Luqi Pei, Ph.D.
PHARM/TOX SUPERVISOR: Timothy McGovern Ph.D.
DIVISION DIRECTOR: Badrul Chowdhury, M.D., Ph.D.
PROJECT MANAGER: Colette Jackson

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Date of review submission to Division File System (DFS): March 26, 2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The nonclinical discipline recommends an approval of the application (NDA 22-203). The application includes adequate nonclinical data to support the safety of _____ (MP03-33), the new sweetened azelastine formulation. The data included intranasal toxicity studies of _____ up to 6 months in rats and dogs. The studies compared the effects of _____ and Astelin[®] (the currently marketed product) on the respiratory system. These studies showed that _____ and Astelin[®] exhibited similar effects.

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B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

The review recommends edits of nonclinical sections of the proposed product label for _____. Format of the proposed label was in compliance with the current Physician's Labeling Rule. The content of the nonclinical sections of the label was adopted from the label of Astelin[®] that is currently on the market. In comparison with Astelin[®] label, the _____ label created new headings [i.e., Use in specific Populations (Section 8) and Nonclinical Toxicology (Section 13)] and subheadings [e.g., Animal Toxicology/ Pharmacology (Section 13.2)]. These headings made it necessary to rearrange the animal findings, although there were no new, relevant nonclinical data that warrants any modifications to the content of the Astelin[®] label.

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Nonclinical sections of the product labeling for _____, the to-be-marketed product, will be adopted from the Astelin[®] Nasal Spray, the currently marketed product, because _____ and Astelin[®] have exactly the same azelastine concentrations and doses, the routes of administration and indications. All nonclinical studies pertinent to the labeling of azelastine were submitted and reviewed previously under the Astelin[®] application (NDA 20-114). The current application contained no studies of genetic toxicity, carcinogenicity, reproductive and developmental toxicity of azelastine, the active ingredient in both _____ and Astelin[®]. Please see Section 2.6.6.1 (Overall Toxicology Summary, page 8) for the Astelin[®] labeling.

The sponsor edited the Pregnancy section to place text regarding the _____ use of _____ Nasal Spray during pregnancy at the beginning of the section. In evaluating the proposed label, edits are recommended to the Pregnancy section to conform to recent recommendations from CDER's SEALD

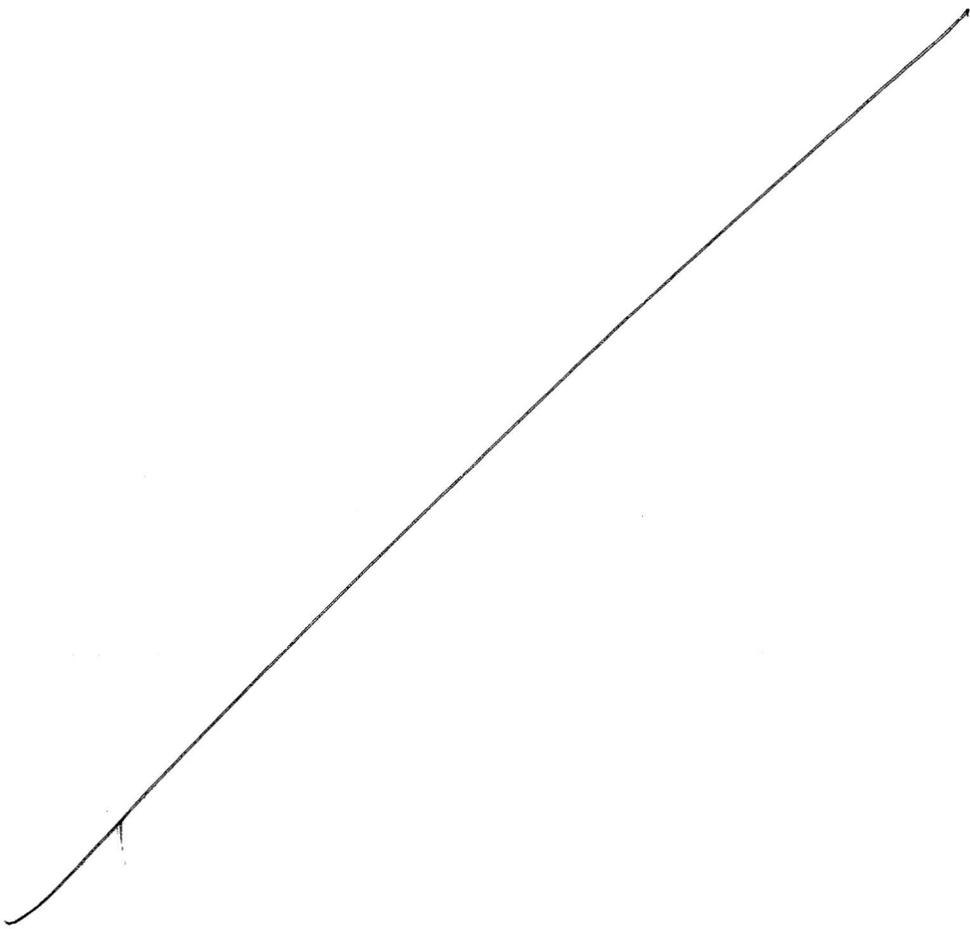
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team. These edits are meant to focus the text on the primary reproductive findings and the animal to human exposure ratios at which they occur to present the most relevant information to the reader. Additional details, such as the actual doses administered, will be presented in Section 13.2: Animal Toxicology and/or Pharmacology - Reproductive Toxicology Studies.

The sponsor's proposed labeling regarding nonclinical sections is presented below. Suggested inserts are presented as underlines and suggested deletions are presented as strikeouts.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy



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10 OVERDOSAGE

B. Pharmacologic activity

No new data was submitted. Azelastine hydrochloride exhibits histamine H₁ - receptor antagonist activity in isolated tissues, animal models, and humans.

_____ Nasal Spray is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in *in vitro* studies.

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C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA Number: 22-203
Review Number : 1
Sequence 000/ 30-JUL-2007/ N
number/date/submission type:
Information to the Sponsor: Yes (), No (x)
Sponsor/or Agent: MedPointe Pharmaceuticals, Somerset, NJ
Manufacturer for Drug Substance: MedPointe Pharmaceuticals, Somerset, NJ
Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Products
Review Completion Date: November 19, 2007

Drug:

Trade Name: _____
Generic Name: Azelastine HCl Nasal Spray
Code Name: MP03-33
Chemical Name: (±)-1-(2H)-phthalazine, 4-[(4-chlorophenyl)methyl-2-
 2(hexahydrol-1-methyl-1H-azepin-4-yl)-, mono-
 hydrochloride
CAS Register Number: N/A
Molecular Form and Weight: C₂₂H₂₄ClN₃O•HCl, 418.4
Structure:



Relevant IND/NDAs/DMFs: NDA 20-114; INDs 32,704 and 69,785
Drug Class: Antihistamine
Intended clinical population: Seasonal allergic rhinitis in patients 5 years and older
 and vasomotor rhinitis in patients 12 years and older
Route of Administration: Nasal spray

Clinical Formulation: A nasal spray consists of 0.1% azelastine, _____% sucralose, _____
 hypromellose _____, _____% edetate disodium, _____% sorbitol _____, _____
 sodium citrate, _____% benzalkonium chloride and purified water. Each actuation of a device
 delivers 0.137 ml of the formulation and 137 µg of azelastine HCl (125 µg azelastine base).

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited
 otherwise.

Studies reviewed within this submission: None.

Studies not reviewed within this submission:

14-day Nasal Irritation Procedure in Rats (Study No. 0437RMS57.002)

14-day Intra-nasal toxicity study in dogs (Study No. 0437RMS57.003)

14-day Nasal Irritation Procedure in Rats (Study No. 16365)

6-month intranasal toxicity study with azelastine and sucralose in Sprague-Dawley rats (Study No. 0460RMS57.001)

This document does not review the above studies because Dr. Luqi Pei, the pharmacology and toxicology reviewer, reviewed them previously under IND 69,785. Please see Pharmacology and Toxicology Reviews #3 and #6 in the IND for detailed information. These reviews, completed on August 17, 2006 and February 20, 2007, respectively, are provided as attachments. Review #6 evaluated a draft report of the 6-month study in rats (Study No. No. 0460RMS57.001), but a written review of the final report is not needed because there was no significant changes between the draft and final reports.

_____ is a reformulation product of the Astelin[®] Nasal Spray, the currently marketed product. _____ attempts to remove the bitter after-taste of Astelin[®]. _____ and Astelin[®] has the same active ingredient (0.1% azelastine HCl), indication, dosage and route of administration. _____ however, uses two new excipients: sucralose (____%) and sorbitol (____%). Sucralose is a novel nasal excipient while the proposed concentration of sorbitol is higher than that present in the currently marketed products. Since the toxicity profile of azelastine has been fully characterized previously in NDA 20-114, the toxicology program of _____ is a bridging program to compare the toxicity of Astelin[®] and _____ and to qualify the novel excipients and formulation. This program consisted of a 6-month intranasal toxicity study in rats and 2-week intranasal studies in dogs. This program was agreed upon after a series of discussions between the Division and MedPointe. A pharmacology/toxicology review completed by Dr. Luqi Pei on August 17, 2006 and minutes of the 08-MAY-2005 meeting and the 08-JUN-2006 telephone conference documented the discussions.

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2.6.2 PHARMACOLOGY**2.6.2.1 Brief summary**

No new data were submitted to this NDA. Azelastine hydrochloride, a phthalazinone derivative and the active ingredient of the application, exhibits histamine H₁-receptor antagonist activity in isolated tissues, animal models, and humans. Histamine has been known to play an important role in allergic rhinitis. A product of azelastine, Astelin[®] (NDA 20-114), is approved and currently marketed for the indication of allergic rhinitis.

2.6.2.2 Primary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.3 Secondary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.4 Safety pharmacology

Not applicable because no data was submitted.

2.6.2.5 Pharmacodynamic drug interactions

Not applicable because no data was submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable because no data was submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Not applicable because no data was submitted.

2.6.4.2 Methods of Analysis

Not applicable because no data was submitted.

2.6.4.3 Absorption

Not applicable because no data was submitted.

2.6.4.4 Distribution

Not applicable because no data was submitted.

2.6.4.5 Metabolism

Not applicable because no data was submitted.

2.6.4.6 Excretion

Not applicable because no data was submitted.

2.6.4.7 Pharmacokinetic drug interactions

Not applicable because no data was submitted.

2.6.4.8 Other Pharmacokinetic Studies

Not applicable because no data was submitted.