

2.6.6.3 Repeat-dose toxicity

Not applicable because no new data were submitted. MedPointe submitted intranasal toxicity studies with the new formulation up to 6-month in treatment duration in rats and dogs. Dr. Luqi Pei reviewed them in the Pharmacology and Toxicology Reviews (Nos. 3 and 6) in IND 69,785. These reviews, completed on August 17, 2006 and February 20, 2007, are provided as attachments.

2.6.6.4 Genetic toxicology

Not applicable because no data was submitted.

2.6.6.5 Carcinogenicity

Not applicable because no data was submitted.

2.6.6.6 Reproductive and developmental toxicology

Not applicable because no data was submitted.

2.6.6.7 Local tolerance

Not applicable because no data was submitted.

2.6.6.8 Special toxicology studies

Not applicable because no data was submitted.

2.6.6.9 Discussions and Conclusion

The nonclinical safety evaluation of the application concentrates on comparing the local effects (i.e., the respiratory system) of two nasal products: (MP03-33) and Astelin[®]. The former is the proposed to-be-marketed product while the latter the currently marketed product. and Astelin[®] have an identical azelastine concentration, dose route of administration, and indication. The sponsor has indicated that will eventually Astelin[®]. , however, contains excipients (i.e. sucralose and sorbitol) that are not present in Astelin[®]. In fact, sucralose is a novel excipient for intranasal administration and the proposed use of sorbitol exceeds that of other approved intranasal products. Based the finding that contains sucralose as a novel excipient and a sorbitol concentration higher than that is present in other approved drug products, the Division requested MedPointe to conduct 6-month intranasal toxicity study in a most appropriate species to show that the novel formulation did not enhance the toxicity profile of the approved formulation.

b(4)

MedPointe completed a 6-month intranasal toxicity of _____ in rats. MedPointe also completed two 14-day intranasal toxicity studies of _____ in rats and dogs (one each). These toxicity studies showed that 1) _____ and Astelin® possess similar toxicity profiles, and 2) there is no nonclinical safety concern about the excipients in _____. Overall, the submitted toxicity studies in animals have adequately evaluated the local effect of the formulation, sucralose and sorbitol. b(4)

2.6.6.10 Tables and Figures

Not applicable because no data was submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable because no data was submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The application has submitted adequate nonclinical safety data to support registration of _____, the proposed product. _____ (MP03-33) is a reformulation of the currently marketed Astelin® Nasal Spray. The reformulation attempts to avoid the bitter after taste reported with Astelin®. _____ and Astelin® have identical azelastine concentrations, doses, the route of administration, and indication. The sponsor indicates that _____ will eventually replace Astelin®. Toxicity studies submitted in the application demonstrated that _____ and Astelin® possess comparable toxicity profiles. There are no nonclinical safety concerns about the intended use of _____. b(4)

Despite many similarities between _____ and Astelin®, there are major differences between the two products. Specifically, _____ contains excipients (i.e. sucralose and sorbitol) that are not present in Astelin®. One of the excipients, sucralose, is a novel excipient for intranasal administration. Also, the sorbitol concentration in MP03-33 is higher than that in other approved drug products.

The formulation characteristics of _____ prompted the Division to request an abbreviated bridging toxicology program to show that the new formulation did not enhance to toxicity profile of Astelin and to qualify the safety of the proposed use of sucralose and sorbitol. This abbreviated program included a 6-month intranasal toxicity study in a most appropriate species to support the registration of the drug based on the results of shorter term studies in 2 species. MedPointe completed and submitted 2- and 26-week intranasal toxicity studies of _____ in rats and a 2-week intranasal toxicity study of the drug in dogs. These toxicity studies showed that 1) _____ and Astelin® possess similar toxicity profiles, and 2) there is no nonclinical safety concern about the excipients in _____. The review finds that the

2.6.4.9 Discussion and Conclusions

Not applicable because no data was submitted.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable because no data was submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable because no data was submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The current application contained no new, significant toxicology data about the toxicity profile of azelastine. The pharmacological and toxicological profile of azelastine has been characterized previously during the development of the currently marketed Astelin[®] Nasal Spray (NDA 20-411). According to the approved labeling of the Astelin[®] Nasal Spray, azelastine is non-genotoxic and non-carcinogenic. Azelastine adversely affects the fetal development when given to female rats and rabbits during pregnancy. These effects have been clearly described in the approved label for Astelin[®]. The lack of any new data related to the toxicity profile of azelastine in the current application precludes any modifications to the approved label. Nonclinical sections of the approved Astelin[®] labeling are as follows:

“Carcinogenesis, mutagenesis and impairment of fertility: In 2-year carcinogenicity studies in rats and mice, azelastine hydrochloride did not show evidence of carcinogenicity at oral doses up to 30 mg/kg and 25 mg/kg, respectively (approximately 240 and 100 times the maximum recommended daily intranasal dose in adults and children on a mg/m² basis).

Azelastine hydrochloride showed no genotoxic effects in the Ames test, DNA repair test, mouse lymphoma forward mutation assay, mouse micronucleus test, or chromosomal aberration test in rat bone marrow.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses up to 30 mg/kg (approximately 240 times the maximum recommended daily intranasal dose in adults on a mg/m² basis). At 68.6 mg/kg (approximately 560 times the maximum recommended daily intranasal dose in adults on a mg/m² basis), the duration of estrous cycles was prolonged and copulatory activity and the number of pregnancies were decreased. The numbers of corpora lutea and implantations were decreased; however, pre-implantation loss was not increased.

Pregnancy Category C: Azelastine hydrochloride has been shown to cause developmental toxicity. Treatment of mice with an oral dose of 68.6 mg/kg (approximately 280 times the maximum recommended daily intranasal dose in adults on a mg/m² basis) caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification and decreased fetal weight. This dose also caused maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal effects occurred at a dose of 3 mg/kg (approximately 10 times the maximum recommended daily intranasal dose in adults on a mg/m² basis).

In rats, an oral dose of 30 mg/kg (approximately 240 times the maximum recommended daily intranasal dose in adults on a mg/m² basis) caused malformations (oligo- and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity. At 68.6 mg/kg (approximately 560 times the maximum recommended daily intranasal dose in adults on a mg/m² basis) azelastine hydrochloride also caused embryo-fetal death and decreased fetal weight; however, the 68.6 mg/kg dose caused severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose of 3 mg/kg (approximately 25 times the maximum recommended daily intranasal dose in adults on a mg/m² basis).

In rabbits, oral doses of 30 mg/kg and greater (approximately 500 times the maximum recommended daily intranasal dose in adults on a mg/m² basis) caused abortion, delayed ossification and decreased fetal weight; however, these doses also resulted in severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose of 0.3 mg/kg (approximately 5 times the maximum recommended daily intranasal dose in adults on a mg/m² basis)."

Formulation/Excipients:

— Nasal Spray (MP03-33) is a reformulation product of the currently marketed Astelin[®] Nasal Spray. The route of administration, azelastine concentration and dose, and indication of the two products are identical. The nonclinical development program of — was to bridge the toxicity profile, primarily the local toxicity of azelastine and the new sweetened formulation. Interest in the formulation was prompted by presence of two excipients: sucralose and sorbitol. Sucralose is a novel excipient for intranasal use while the proposed use of sorbitol exceeds the previous use in an intranasal product.

MedPointe conducted a bridging toxicology program that included intranasal toxicity studies of — up to 6 months in rats and 2 weeks in dogs to support the reformulation based on discussions with the Division. Table 1 provides an overview of toxicity studies. They showed that 1) — (i.e., the new formulation) and Astelin[®] Nasal Spray possess similar toxicity profiles; and 2) there is no nonclinical safety concern about the excipients in —. The following summary is based on the Pharmacology and Toxicology Reviews (Nos. 3 and 6) by Dr. Luqi Pei in IND 69,785 and the approved labeling of the currently marketed Astelin[®] Nasal Spray (NDA 20-114).

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Table 1 Overview of Intranasal Toxicity Studies of _____

Study	Species	Duration (week)	Group ^a	n/sex /group
001 ^b	Rat	26	V ^c , Astelin, _____	20
002	Rat	2	R; and _____, R + 0.05%, or	10
003	Dog	2	0.15% SUC	3

a. Each animal received the intended treatment at 0.1 ml/nostril, bid.

b. The study also includes arm for another formulation in development.

c. V = the vehicle for _____, R = reference (_____ minus sucralose); SUC = sucralose

Two 14-day intranasal toxicity studies were completed to compare the effect of _____ on the respiratory tract in rats and dogs (one each, Studies 0437RM57.002 and 003). The two studies had identical study designs except for the sample size: 10 and 3/sex/group in rats and dogs, respectively. One-tenth of 1 ml/nostril of _____ or a reference solution (control) was instilled into the nasal cavity of Sprague-Dawley rats or beagle dogs twice a day for 14 days. The reference solution (or control) contained 0.1% azelastine, _____% hypromellose _____% edetate disodium, _____% sorbitol, _____% sodium citrate, and _____% benzalkonium chloride. Two additional groups were given _____ with slightly different sucralose concentrations: 0.05% and 0.15% respectively. The results showed that azelastine was slightly irritating to the nasal mucosa. The addition of sucralose at concentrations up to 0.15% to the reference solution (0.1% azelastine plus non-sucralose excipients), however, did not increase the incidence of irritation to or abnormalities in the nasal cavity in rats or dogs.

A 6-month intranasal toxicity study of _____ (Study 0460RM57.001) was conducted in rats. Choice of species for the chronic toxicity study was agreed upon with the sponsor at a meeting in August 2006. Sprague-Dawley rats (20/sex/group) were treated with the vehicle for _____ Astelin[®], or MP03-36 (another azelastine formulation) twice daily for 26 weeks. The azelastine concentration was 0.1%, 0.1% and 0.15% in _____ Astelin[®], and MP03-36, respectively. Prevalent mucosal inflammation and goblet cell hyperplasia in the nasal cavity were observed in all groups. The incidence of these changes was similar among the vehicle, _____ and Astelin[®] groups. The respective incidence of mild inflammation for the vehicle, Astelin, and _____ was 8/40, 5/40, 6/40 in the Level 1 area of the nasal cavity and 6/40, 7/40, and 8/40 in the Level 2 area. The results showed that _____ and Astelin[®] had comparable toxicity profiles.

The above data show that Astelin[®] and _____ possess similar toxicity profiles. The addition of sucralose as a novel excipient and sorbitol at higher levels than previously used in intranasal products does not affect the safety profile of intranasally administered azelastine.

2.6.6.2 Single-dose toxicity

Not applicable because no data was submitted.

nonclinical data have adequately addressed nonclinical requirements for registration of _____ The review recommends the approval of the application from the nonclinical perspective.

Unresolved toxicology issues (if any): None.

Recommendations:

Approval of the _____ is recommended from the nonclinical discipline.

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Suggested labeling:

Nonclinical sections of the labeling of _____ will be adopted from the Astelin[®] Nasal Spray, the currently marketed product. _____ and Astelin[®] have exactly the same azelastine concentration and dose. Their routes of administration and indication are also the same. The current application contains no new genetic toxicity, carcinogenicity, reproductive and developmental toxicity studies of azelastine, the active ingredient for both products. All nonclinical studies pertinent to the labeling of azelastine were referenced to the Astelin[®] application (NDA 20-114). Any revisions to the information in the already approved labeling are not warranted due to the lack of new data. However, the sponsor has reformatted the product label to conform to the PLR recommendations. Some suggested revisions are recommended to conform the Pregnancy section of the label with recent recommendations made by CDER's SEALD team. See the recommended labeling changes indicated in the Executive Summary of this review.

ATTACHMENTS

- A. Pharmacology and Toxicology Review #3 by Dr. Luqi Pei completed on August 17, 2006 in IND 69,785.
- B. Pharmacology and Toxicology Review #6 by Dr. Luqi Pei completed on February 20, 2007, in IND 69,785.

ATTACHMENT A

**Pharmacology and Toxicology Review #3
by Dr. Luqi Pei completed on August 17, 2006 in IND 69,785.**

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

IND Number: 32,704 and 69,785
Review Number: 3
Sequence No./Date/ Submission Type:

	<u>IND 32,704</u>	<u>IND 69,785</u>
	091/ 21-FEB-05/ IT	002/ 18-FEB-05/ IT
	094 / 03-JUN-05/ IT	009/ 02-JUN-05/ IT
	099/ 16-FEB-06/ IT	015/ 13-FEB-06/ IT
		016/ 03-MAR-06/ PN, IC

Information to the Sponsor: None
Sponsor/or Agency: MedPointe Pharmaceuticals, Somerset, NJ
Manufacturer of the Drug: MedPointe Pharmaceuticals
Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Products
Review Completion Date: August 17, 2006
Drug:

Trade Name:	Astelin [®] Nasal Spray
Generic Name:	Azelastine HCl
Code Name:	MP03-33

Clinical Formulations: 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 (Source: Serial No. 016, vol. 8.1, p 181). Table 1 provides the amount of each component delivered per actuation.

Table 1 Amount of Ingredients Delivered per Actuation

Inactive Ingredient	Concentration (%)	µg/actuation
Azelastine	0.1	137
Sorbitol _____, USP	_____	_____
Sucralose, NF	_____	_____
Hypromellose, USP	_____	_____
Edetate disodium, USP	_____	_____
Sodium citrate, USP	_____	_____
Benzalkonium chloride, NF _____	_____	_____

Proposed Clinical Protocol: Approximately 780 male and female patients 12 years and older will be using 1 or 2 sprays/nostril of Astelin[®], MP03-33 (a new formulation), or vehicle for MP03-33 twice a day for 2 weeks. Each actuation of Astelin[®] or MP03-33 delivers 137 mcg of azelastine HCl. The protocol is entitled "Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of MP03-33 in Patients with Seasonal Allergic Rhinitis (Protocol No. MP430).

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