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RESEARCH**

APPLICATION NUMBER:

22-203

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-203
Type:	Class 1 Resubmission
Brand Name (proposed):	Astepro® (_____) was initially proposed but determined unacceptable)
Generic Name:	Sweetened Azelastine Hydrochloride
Indication:	Seasonal allergic rhinitis for adults and children ≥ 12 yrs
Dosage Form:	Metered-spray solution
Strength:	137 mcg / 0.137 mL per spray
Route of Administration:	Nasal spray
Dosing regimen:	1 or 2 sprays per nostril twice daily
Applicant:	MedPointe Pharmaceuticals
OCP Division:	DCP2
Clinical Division:	DPAP (OND-570)
Submission Date:	August 14, September 17, 2008
Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Wei Qiu, Ph. D.

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BACKGROUND

In the original NDA submission, the applicant was seeking approval of _____^M for the relief of symptoms of seasonal allergic rhinitis (SAR) in patients 5 years of age and older and vasomotor rhinitis (VMR) for 12 years of age and older. The Division of Pulmonary and Allergy Drug Products (DPAP) concluded the following: 1) the applicant has submitted adequate data to support approval of (b) (4) _____ for the relief of symptoms of SAR in patients 12 years of age and older; 2) the submitted data do not support approval for SAR in patients 5 to 11 years of age, and 3) the submitted data also do not support approval for VMR in patients 12 years of age and older, and 4) _____ in the proposed label is not supported because there is _____ for the _____.

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The overall action on this application was *Not Approval*. As a result, the applicant filed a formal dispute resolution request (FDRR) for non-approval of SAR and VMR indications for patients ≥ 5 years and ≥ 12 years of age, respectively, and denial of _____ in the proposed labeling. In his response to the FDRR, the Office of Drug Evaluation II director Dr. Curtis Rosebraugh concluded that although DPAP was all along convinced of the safety and efficacy of the applicant's product for the SAR indication in patients 12 years and older, it was not approved primarily due to labeling impasse, which was inappropriately not cited at the time of regulatory action and hence resulted in miscommunication between the DPAP and the applicant (refer to Dr. Rosebraugh's response to FDRR dated 08/07/2008). Based on this conclusion, Dr. Rosebraugh requested the applicant to resubmit the application as a Class 1 re-submission for the indication of SAR for ages 12 years and older for approval provided appropriate labeling can be agreed upon between the DPAP and the applicant.

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Following this response, the applicant resubmitted the NDA under a new drug name (Astepro®). This submission is seeking approval of Astepro® for the relief of symptoms of SAR in patients 12 years of age and older. The applicant narrowed the SAR patient population age to 12 years and above while the VMR indication was dropped.

1. EXECUTIVE SUMMARY

The Clinical Pharmacology content of the NDA remained unchanged from the original submission for ~~_____~~⁴. This has been reviewed in the first cycle (Refer to Clinical Pharmacology Review by Dr. Partha Roy dated 3/28/08) and found acceptable. The applicant has included the suggested initial labeling changes. In this review cycle, the Division of Clinical Pharmacology-2 has some additional labeling comments.

1.1 LABELING REVIEW

Under section 12.3 **Pharmacodynamics**, the following text appeared from the original approved Astelin® label: "At higher oral exposures (>4 mg twice daily), a nonclinically significant mean change on the QTc (3-7 millisecond increase) was observed." The use of the term "nonclinically significant change" to qualify QTc change was judged unclear at the present time. However, at the time of Astelin® approval back in 1995, it was felt that the word "nonclinically significant" was important to be included in order to reassure the prescribing physicians that only a weak effect on cardiac repolarization exists at a substantially higher systemic exposure compared to that from intranasal administration in the clinic (refer to Medical Officer's review of Astelin® Cardiac safety data by Dr. Peter Honig dated May 17, 1995, page 203 of 1536 of the N20-114 Action Package).

Based on Dr. Peter Honig's review, it was determined that azelastine has an effect on cardiac repolarization at oral doses that are markedly higher than the approved intranasal dose used in the clinic. However, no consistent dose-effect relationship was found as shown in the following table adopted from Dr. Honig's review dated May 17, 1995.

Multiple-Dose Group Analysis:

Treatment Arm	Change in QTc		Percent Change in QTc	
	Mean Change	p Value*	Mean % Change	p Value*
< 1 mg (n=53)	4.22	.50	1.17	.59
2 mg (n=75)	1.36	.96	.58	.95
4 mg (n=248)	7.22	.017	2.01	.02
6 mg (n=35)	5.20	.44	1.55	.44
8 mg (n=12)	3.57	.79	1.27	.74
Placebo (n=237)	1.53	-	.63	-

*vs Placebo

Based on the above data and discussion, the following new text is proposed from the Division of Clinical Pharmacology-2 under section 12.3 **Pharmacodynamics** to replace the old text stated above.

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In addition, the paragraph entitled "Asthmatic Patients" should be moved from section 12.3 **Pharmacokinetics** to section 8 **USE IN SPECIFIC POPULATIONS** to read as follows:

8.6 Asthmatic Patients

Oral azelastine has been safely administered to over 1400 asthmatic subjects, supporting the safety of administering azelastine hydrochloride nasal spray to allergic rhinitis patients with asthma.

The above two recommendations were communicated to DPAP (Colette Jackson, Sally Seymour and Susan Limb) via an email on September 28, 2008. While the recommendation for moving the text related to asthmatic patients to section 8.6 was adopted as is, the Division modified the recommended text for section 12.3 and conveyed to the applicant to incorporate the following in the final label:

Following multiple dose oral administration of azelastine 4 mg or 8 mg twice daily, the mean change in QTc was 7.2 msec and 3.6 msec, respectively.

No action is needed at this time.

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/s/

Partha Roy
10/15/2008 01:30:39 PM
BIOPHARMACEUTICS

Wei Qiu
10/15/2008 01:32:52 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-203
Type:	Original
Brand Name (proposed):	_____ M
Generic Name:	Sweetened Azelastine Hydrochloride
Indication:	Seasonal allergic rhinitis for adults and children ≥ 5 yrs; Vasomotor rhinitis for adults and children ≥ 12 yrs.
Dosage Form:	Metered-spray solution
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Route of Administration:	Nasal spray
Dosing regimen:	1 or 2 sprays per nostril twice daily
Applicant:	MedPointe Pharmaceuticals
OCP Division:	DCP2
Clinical Division:	DPAP (OND-570)
Submission Date:	July 30, 2007
Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Wei Qiu, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-203's Clinical Pharmacology information submitted on July 30, 2007 and finds it acceptable provided that a satisfactory agreement is reached between the applicant and the Agency regarding the proposed new language to be included in the package insert.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor submitted a 505(b)(1) application for a sweetened formulation of azelastine hydrochloride nasal spray with a proposed trade name of _____. An unsweetened formulation (Astelin®) is currently marketed. Due to a distinctive bitter taste that limits marketing of Astelin® and patient compliance, the sponsor has developed a sweetened intranasal azelastine formulation (_____^M), containing two novel additional excipients, sucralose and sorbitol. The clinical development program consists of new clinical studies to demonstrate clinical comparability and safety between the sweetened and unsweetened formulations, including a relative bioavailability study in healthy male subjects (MP429), 2 week efficacy and safety study in patients with SAR (MP430) and a 6-month safety study (MP432). The proposed indications and dosages for _____^A are the same as those of the commercial product, Astelin®. The purpose of the relative bioavailability study is to support systemic safety of the drug product.

The sponsor evaluated single-dose pharmacokinetics (PK) of azelastine and its major active metabolite, desmethylazelastine in an open-label, single-center, randomized, parallel group relative bioavailability study in which 18 healthy male subjects ages 18-50 years were treated with one of three intranasal formulations (2 sprays per nostril) of azelastine hydrochloride: Treatment A: commercial formulation of 0.1% Astelin® (total dose: 548 mcg), Treatment B: proposed new formulation of 0.1% _____^M (total dose: 548 mcg) and Treatment C: higher strength formulation of 0.15% _____^M (total dose: 822 mcg). The intent of the study was not to pursue bioequivalence, but to assess comparative bioavailability between the proposed and marketed formulations. This study becomes particularly important because sorbitol, present in the _____^M formulation, is not included in the marketed Astelin® formulation and has been known to affect absorption of drugs following oral administration; however its effect on drug absorption following intranasal administration is unknown.

Relative bioavailability between _____^A and Astelin®:

The PK parameters of azelastine and desmethylazelastine following intranasal administration of 0.1% _____^A and 0.1% Astelin® are listed in Table 1 below. Azelastine was found to be

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absorbed into the systemic circulation with a median T_{max} of 3 hours following single dose intranasal administration of [redacted]. The mean (SD) terminal half-life values of azelastine and desmethylazelastine were calculated to be 22 (7.5) hrs and 52 (21) hrs, respectively. The data revealed that systemic exposure of azelastine and desmethylazelastine, as evidenced by mean C_{max} , AUC_{0-t} and AUC_{0-inf} , from [redacted] was numerically slightly lower compared to Astelin®. All other pharmacokinetic parameters including time to peak plasma concentration (T_{max}), elimination half-life ($T_{1/2}$), intranasal clearance (CL/F) were comparable between the two formulations.

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Table 1. Mean \pm SD pharmacokinetic parameters of azelastine and desmethylazelastine following 2 sprays of 0.1% Astelin® and 0.1% [redacted] solution per nostril

PK parameters	Azelastine		Desmethylazelastine	
	Astelin® (marketed)	[redacted] (new)	Astelin® (marketed)	[redacted] (new)
AUC_{0-t} (pg.hr/mL)	5903 \pm 2264	4917 \pm 1394	1873 \pm 553	1634 \pm 603
AUC_{0-inf} (pg.hr/mL)	6122 \pm 2373	5122 \pm 1546	2615 \pm 779	2131 \pm 609
C_{max} (pg/mL)	235 \pm 88	200 \pm 67	24 \pm 7.8	23 \pm 11
T_{max} (hr)*	4.0 (0.25-6.0)	3.0 (0.5 – 4.0)	24 (24-72)	24 (12 – 96)
$T_{1/2}$ (hr)	24 \pm 6.0	22 \pm 7.5	60 \pm 22	52 \pm 21
CL/F (mL/min/kg)	25 \pm 18	26 \pm 9.5	53 \pm 24	61 \pm 16

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* median (range)

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Dose proportionality of [redacted]:

The dose and bodyweight normalized mean C_{max} and AUC_{0-inf} values of azelastine and desmethylazelastine were found to be slightly higher for the 0.15% [redacted] (total dose: 822 mcg) compared to 0.1% [redacted] (total dose: 548 mcg). Therefore, [redacted] exhibits a slightly greater than dose proportional pharmacokinetics across the dose range of 548 mcg and 822 mcg.

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Conclusions

The pharmacokinetic data from study MP429 revealed that systemic exposures of azelastine and desmethylazelastine from [redacted] were numerically slightly lower compared to Astelin®. Although the higher dose (822 mcg) of [redacted] tends to exhibit a slightly greater than dose proportional exposure relative to its therapeutic dose (548 mcg), dose normalized systemic exposure from the higher dose of (b) (4) [redacted] and therapeutic dose (548 mcg) of Astelin® are generally comparable (Figures 2 and 3 in section 2.2.1.).