



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-203

MedPointe Pharmaceuticals
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Michael I. Bernhard, PhD.
Senior Director, Regulatory Affairs

Dear Dr. Bernhard:

Please refer to your July 30, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (azelastine hydrochloride) Nasal Spray, 137 mcg.

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We also refer to your submission dated August 16, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on September 28, 2007, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. However, we do have the following comments.

- 1. The adequacy of the application to support a vasomotor rhinitis (VMR) indication will be a review issue.

[Redacted text block]

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- 2. Study [Redacted]

- 3. On the carton and container labels, remove the graphic above the proprietary name as it obscures and crowds the proprietary name. In addition, by

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/s/

Badrul Chowdhury
10/12/2007 02:19:16 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,785

MedPointe Pharmaceuticals, MedPointe Healthcare, Inc.
265 Davidson Avenue
Suite 300
Somerset, NJ 08873-4120

Attention: Richard Fosko, RPh
Associate Director, Regulatory Affairs

Dear Mr. Fosko:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Astelin (azelastine hydrochloride) Nasal Spray.

We also refer to your September 20, 2005, request, serial number 013, for a special clinical protocol assessment, received September 21, 2005. The protocol is entitled "Randomized, Double-Blind, Placebo-Controlled Trial of a Reformulated Astelin® (azelastine hydrochloride) Nasal Spray Compared to the Original Astelin® Formulation in Patients with Seasonal Allergic Rhinitis".

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions (in bold italics)

1. ***Does the Division agree that the proposed study design in protocol MP430 meets the guidance provided in our May 3, 2005 discussion?***

Response:

The general concept for the study design is acceptable; however, the decision on approvability can only be rendered upon review of the NDA.

2. ***Does the Division agree with the proposed blinding strategy in protocol MP430?***

Response:

No, the Division does not agree. The proposed study design has not adequately blinded the active drug groups receiving two sprays per nostril twice daily from the placebo group. As there is no placebo being dosed as two sprays per nostril twice daily, the investigators and possibly the patients would know that patients receiving two sprays of study treatment were assigned to active drug. One

approach for achieving better blinding could be to have four placebo groups mimicking the four active groups (i.e., one spray and two sprays of the old formulation placebo and one spray and two sprays of the new formulation placebo with sucralose). Each placebo group could be ¼ the size of the currently planned placebo group. The efficacy of the placebo groups could be compared amongst them and if not appreciably different, combined for the overall treatment to placebo comparisons of efficacy and safety. The protocol should include a description of how the similarity of the placebo groups would be assessed/tested.

3. *In clinical Study MP430, onset of action will be evaluated for each of the two doses of the new formulation and current formulation versus placebo. Onset of action for each dose of each formulation will be evaluated in approximately 125 patients per arm.*

Does the Division agree with the position?

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Response:

No, we do not agree. Evaluation of the two doses of the new formulation and the current formulation will not satisfy the requirement for replication in two studies.

In addition, we have the following comments.

1. We acknowledge that you have agreed to submit two 2-week intranasal toxicity studies prior to initiation of proposed study MP430.
2. You will also need to conduct a separate clinical safety program to support the safety of the reformulated product prior to submission of your New Drug Application.
3. Although you provided draft labeling and anticipated promotional claims, no concurrence can be given to these elements at this time. Evaluation of labeling and promotional claims is a review issue that will be addressed after the NDA has been submitted.
4. You are reminded that a positive intradermal test is one that is 7 or more mm greater than the negative control and not 7mm or greater as you have proposed. Refer to the Draft Guidance for Industry: *Allergic Rhinitis: Clinical Development Programs for Drug Products*.
5. The protocol states that "Missing TNSS values will be imputed using the last observation carried forward." We interpret this as the LOCF will be applied to missing post-treatment outcomes. Clarify if this is the method which is intended to be used for intermittently missing data during the baseline period. Also, specify how TNSS will be calculated if individual symptom scores are missing.

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6. The protocol indicates that treatment randomization data will be kept confidential, accessible only to authorized persons, until the time of unblinding. Please explain. Our expectation is that no one should have access to the randomized data until the study is unblinded except for individual patient data in the context of a serious safety concern.
7. You should consider adding the center effect in your model as randomization is within centers. At the very least you should assess differences between centers by graphical or other means.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our “*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*”). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,
{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
11/4/2005 03:49:19 PM



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: June 9, 2005

To: Richard Fosko	From: Colette Jackson
Company: Medpointe Pharmaceuticals	Division of Pulmonary and Allergy Drug Products
Fax number: 732-564-2361	Fax number: 301-827-1271
Phone number: 732-564-2358	Phone number: 301-827-9388

Subject: IND 69,785 May 3, 2005, Meeting Minutes

Total no. of pages including cover:

Comments: Protocol comments

Document to be mailed: YES NO

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IND 69,785

Drug: Azelastine Hydrochloride Nasal Spray

Sponsor: MedPointe Pharmaceuticals

Date of Meeting: May 3, 2005

MedPointe Representatives:

Richard N. Spivey, Pharm D, Ph.D., Senior Vice President, Research & Development

Alexander D. D'Addio, Ph.D., Vice President, Product & Process Development

Harry J. Sacks, M.D., Senior Director, Medical Affairs

Michael Bernhard, Ph.D., Senior Director, Regulatory Affairs

William Wheeler, Ph.D., Director, Medical Communications

Carol R. Sax, Associate Director, Regulatory Affairs

Richard Fosko, R.Ph., MPH, Associate Director, Regulatory Affairs

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Division of Pulmonary & Allergy Drug Products Representatives:

Badrul A. Chowdhury, M.D., Ph.D., Agency Director

Tejashri Purohit-Sheth, M.D., Clinical Reviewer

Lydia Gilbert-McClain, M.D., Medical Team Leader

Warner Carr, M.D., Clinical Reviewer

Sandra Suarez, Ph.D., Clinical Pharmacology/Biopharmaceutics

Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader

Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer

Timothy McGovern, Ph.D., Pharmacology/Toxicology Team Leader

James Gebert, Ph.D., Statistical Reviewer

Colette Jackson, Project Manager

Background: MedPointe submitted a meeting request dated February 25, 2005, to discuss their proposed clinical program for a sweetened Azelastine hydrochloride nasal spray formulation. MedPointe submitted a briefing package containing questions to be discussed at this meeting on April 4, 2005, and an additional question was submitted on April 6, 2005. The Division responded to those questions by sending a telephone facsimile dated April 29, 2005. The content of this telephone facsimile is printed in Italics below. Any discussions are captured directly under each response in normal font.

Clinical Program

Question A. Does the Division agree that a single clinical SAR study per the Draft Guidance and as outlined in our Protocol Concept Sheet is appropriate to evaluate clinical comparability between the currently marketed Astelin Nasal Spray formulation and the sweetened formulation?

Response: A single clinical SAR study as outlined in the initial protocol submitted, evaluating two doses of both the new and old formulations and placebo (5-treatment arm study), is appropriate to evaluate clinical comparability of the two formulations. We suggest you add pharmacokinetic assessments as recommended in the Draft Guidance for Allergic Rhinitis.

Additional Design Comment

The 3-treatment arm alternate proposed study design would not suffice to demonstrate clinical comparability as it would not compare the dose-response curves of the reference and sweetened formulations or to meet the stand-alone approach either, as this design is not for a dose-ranging study.

Question B. Assuming clinical comparability is demonstrated in a single SAR study, does the Division agree this is sufficient basis for approval of the sweetened formulation for the treatment of SAR symptoms in patients 5 years of age and older?

Response: Yes. However, demonstration of clinical comparability should be convincing. Note that whether clinical comparability is demonstrated will be a review issue.

Question C. Assuming clinical comparability is demonstrated in a single SAR study, does the Division agree that this is sufficient basis for approval of the sweetened formulation for the treatment of VMR in patients 12 years of age and older?

Response: A single SAR study convincingly demonstrating comparability of the two formulations may be sufficient for carrying over the VMR indication to the sweetened formulation.

Discussion:

MedPointe requested clarification of the Division's responses in order to resolve their design issues. The Division referred to the Guidance for Industry, "Allergic Rhinitis: Clinical Development Programs for Drug Products" (draft guidance, April 2000), which outlines two approaches—comparability and the stand alone approach. With the comparability approach, it is required that dose response curves are comparable. MedPointe requested clarification on what the Agency meant by comparable. The Division responded that the comparability approach includes evaluating dose response curves for at least two doses of the old and new formulations. MedPointe referred to the draft guidance, noting it requires comparison to approved doses, for which MedPointe only has 1 approved dose. The Division stated that comparing one dose of each formulation would not work as the Division is assuming that Q_1 and Q_2 are different, as defined in the Nasal BA/BE Guidance (Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003). Therefore, MedPointe should use whatever doses it needs to for comparison of two doses of each formulation. The Division also emphasized that the proposed 5-treatment arm design is most

compatible with the comparability approach, and whether clinical comparability is established will be a review issue.

MedPointe also requested clarification on the primary comparison. They propose a design which is statistically powered to compare active treatment versus placebo. They do not intend to power the study to compare the old and new formulations as the primary comparison nor show that the formulations are not statistically different. The Division responded that this is acceptable. The Division does not intend for the sponsor to demonstrate Bioequivalence as stated in the Nasal BA/BE guidance (“Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action”, April 2003). The Division will evaluate from a non-statistical standpoint whether the two formulations are similar. If the old or new formulations appear similar to placebo, then there would be a problem with the study and subsequent interpretation of study results. The Division also stated that the relative potency of the two products should be estimated from the data of the active products only and not placebo. It was also recommended that MedPointe include baseline as covariate in the model.

MedPointe also stated that Baseline will be defined as results from the 1-week run-in period. The Division responded that this is acceptable. Furthermore, the Division stated that MedPointe may consider not allowing patients who respond to placebo during the run-in period to enter the treatment period of the study if they want to show discriminatory results since it is not unreasonable to use such an enrichment design by having minimum entry requirements based on placebo response during the run-in period.

In summary, MedPointe stated they will use the comparability approach for their clinical study design, to include 5 treatment arms. They will compare active treatment versus placebo for statistical purposes, and they will eyeball the dose response curves for the two active treatment comparisons. They will estimate the relative potency of the two products using data from the active products and not use placebo in their calculations.

Pharmacokinetic Requirements

Question: Does the Division agree that no additional pharmacokinetic evaluations are required for the sweetened formulation?

Response: No. The new formulation contains ingredients (such as sorbitol) that may change the bioavailability of the drug. Therefore, it is recommended that you assess the pharmacokinetics of the drug and its metabolites following nasal administration of the to-be-marketed product. This can be accomplished by taking blood samples to describe the full PK profile from a subgroup of patients enrolled in your proposed clinical trial, or by conducting a stand alone PK study.