CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-371s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
22-371

NAME OF APPLICANT / NDA HOLDER
MEDA Pharmaceuticals
MEDA Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
TRADENAME Nasal Spray

ACTIVE INGREDIENT(S)	STRENGTH(S)
azelastine hydrochloride	205.5 mcg

DOSAGE FORM
Nasal Spray

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,164,194	11/17/1992	11/1/2010

d. Name of Patent Owner
MEDA Pharmaceuticals
MEDA Pharmaceuticals Inc.

Address *(of Patent Owner)*
265 Davidson Ave, Suite 300

City/State
Somerset, NJ

ZIP Code	FAX Number *(if available)*
08873-4120	732-564-2377
Telephone Number	**E-Mail Address *(if available)***
732-564-2358	rfosko@medapharma.us

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code	FAX Number *(if available)*
Telephone Number	**E-Mail Address *(if available)***

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Patent Claim Number *(as listed in the patent)* 1,2,3,4,5,6,7,8,9,12 — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. — Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*		

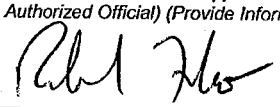
5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	7/22/2008

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Richard Fosko, RPh., MPH Director, Regulatory Affairs MEDA Pharmaceuticals Inc.	
Address 265 Davidson Ave, Suite 300	City/State Somerset, NJ
ZIP Code 08873-4120	Telephone Number 732-564-2358
FAX Number *(if available)* 732-564-2377	E-Mail Address *(if available)* rfosko@medapharma.us

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-371 SUPPL # HFD # 570

Trade Name Astepro

Generic Name azelastine hydrochloride 0.15%

Applicant Name MEDA Pharmaceuticals

Approval Date, If Known August 31, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22-203 Astepro

NDA# 20-114 Astelin

NDA# 21-127 Optivar

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

MP433, MP434, and MP438

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study MP433, MP434, and MP438

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 69,785	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 69,785	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Colette Jackson
Title: Senior Regulatory Health Project Manager
Date: August 13, 2009

Name of Office/Division Director signing form: Badrul A. Chowdhury
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

COLETTE C JACKSON
08/31/2009

BADRUL A CHOWDHURY
08/31/2009

MEDA PHARMACEUTICALS™

June 16, 2008

NDA 22-371

Azelastine Hydrochloride 0.15% w/v Nasal Spray

DEBARMENT CERTIFICATION STATEMENT

Meda Pharmaceuticals (formerly MedPointe) hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the above application.

Veronica Donner
Meda Pharmaceuticals
Manager, Corporate Quality Assurance

06/17/08
Date

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

A/BLA#: 22-371 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:Pulmonary and Allergy Products PDUFA Goal Date: June 1, 2009 Stamp Date: August 1, 2008

Proprietary Name: Dymysta

Established/Generic Name: azelastine hydrochloride 0.15%

Dosage Form: Nasal Spray

Applicant/Sponsor: Meda Pharmaceuticals

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Seasonal Allergic Rhinitis

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☒ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☒ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	0 yr. __ mo.	2 yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☒ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

+ Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	2 yr. __ mo.	11 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† *Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies - a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)*

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☒	Other	12 yr. __ mo.	16 yr. __ mo.	Yes ☐	No ☒
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

ditional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☒	Other	12 yr. __ mo.	16 yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

ıication #2: Perennial Allergic Rhinitis

Q1: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☒ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria belo

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. __ mo.	__ yr. 6 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☒ Necessary studies would be impossible or highly impracticable because:

- ☒ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

ction C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	__ yr. 6 mo.	11 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☒	Other	12 yr. __ mo.	16 yr. __ mo.	Yes ☐	No ☒
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

ction F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

e the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

'Revised: 6/2008)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-371 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Astepro 0.15% Established/Proper Name: azelastine hydrochloride 0.15% Dosage Form: Nasal Spray		Applicant: Meda Pharmaceuticals Agent for Applicant (if applicable):
RPM: Colette Jackson		Division: 570 Pulmonary and Allergy Products

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	June 1, 2009 September 1, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 5S

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	April 29, 2009
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s): August 31, 2009
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	August 26, 2009
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	August 28, 2009
• Original applicant-proposed labeling	August 1, 2008
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☒ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	August 8, 2009
• Most recent applicant-proposed labeling	August 17, 2009
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM April 22, 2009 ☒ DMEDP May 5, and 8, and August 4, 2009 ☒ DRISK April 29, 2009 ☒ DDMAC February 17, 2009 ☐ CSS ☒ Other reviews SEALD review April 24, 2009
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 May 8, 2009 May 8, 2009
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	April 22, 2009
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	April 20, July 30, and August 25, and 27, 2009
❖ Postmarketing Commitment (PMC) Studies	☒ None

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	August 27, 2009
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	August 21,and October 14, 2008, and January 6, March 20, March 31, May 1, 4, 8, and 19, July 17, August 8, 14, and 26, 2009
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable April 29, 2009
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☐ No mtg August 29, 2006
• Other (e.g., EOP2a, CMC pilot programs)	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None August 31, 2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None April 20, 2009
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Contained in CDTL review dated April 20, 2009
• Clinical review(s) *(indicate date for each review)*	October 6, 2008, and April 1, and July 15, 2009
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	April 1, 2009 and July 15, 2009
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	April 1, 2009
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

• REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None April 10, and July 17, 2009
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None September 26, 2008, and April 13, 2009
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None March 26, and July 8, 2009
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None September 17, 2008, and March 16, April 20, and June 24, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None March 11, 2009
• CMC/product quality review(s) *(indicate date for each review)*	☐ None September 15, 2008, and March 11, and April 17, 2009
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)*	☒ Not needed

• BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	March 11, 2009
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: March 18, 2009 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22371	ORIG 1	MEDA PHARMACEUTICALS INC	AZELASTINE HYDROCHLORIDE NASAL SPRAY

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

COLETTE C JACKSON
09/01/2009

Memorandum

To: NDA# 22-371, Astepro (azelastine hydrochloride) Nasal Spray 0.15%
NDA# 22-203, Astepro (azelastine hydrochloride) Nasal Spray 0.1%

From: Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary and Allergy Products

Regarding: Post-Marketing Requirements Templates

Date: August 31, 2009

NDA# 22-371 is for a new strength (0.15%) sweetened azelastine nasal spray for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older and for the treatment of symptoms of perennial allergic rhinitis (PAR) in patients 12 years of age and older. An unsweetened azelastine nasal spray is currently approved for the treatment of symptoms of SAR and vasomotor rhinitis (VMR) under the tradename Astelin Nasal Spray (NDA# 20-114). A sweetened formulation of azelastine nasal spray 0.1% was approved on October 15, 2008, under the tradename Astepro Nasal Spray (NDA# 22-203) for the treatment of symptoms of SAR in patients 12 years of age and older. This application provides for a higher strength 0.15% formulation of Astepro Nasal Spray for the treatment of SAR and PAR in patients 12 years of age and older.

PREA is triggered by this application because Astepro Nasal Spray 0.15% provides for a new indication (PAR) and a new dosing regimen of once daily for the treatment of SAR. Pediatric studies have been deferred for the following indications:

- Seasonal allergic rhinitis in patients 2 years to < 12 years of age. *Studies under the age of 2 years are waived as SAR is not considered to exist in patients below 2 year of age.*
- Perennial allergic rhinitis in patients 6 months to < 12 years of age. *Studies under the age of 6 months are waived as PAR is not considered to exist in patients below 6 months of age.*

MEDA submitted a pediatric program of 4 clinical trials to address the PREA requirements. The program includes the development of an age appropriate formulation for the younger age groups. The Division is generally in agreement with the proposed pediatric program to address the PREA requirements. This document provides the templates for the 4 post-marketing PREA requirements.

Both strengths of Astepro Nasal Spray will be incorporated under NDA# 22-203 in the future; therefore, this document will be attached to both applications for completeness.

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA for the treatment of perennial and/or seasonal allergic rhinitis in pediatric patients ages 6 years to less than 12 years of age.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	11/31/2009
	Study/Clinical trial Completion Date:	06/30/2011
	Final Report Submission Date:	12/31/2011
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Pediatric study was deferred because the adult and adolescent program was completed and ready for approval. The adult and adolescent program provided adequate safety data to support studies in pediatric patients < 12 years of age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Evaluate the safety and efficacy of Astepro Nasal Spray in patients 6 years to < 12 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical trial in patients 6 years to < 12 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA for the treatment of perennial and/or seasonal allergic rhinitis in pediatric patients ages 6 months to less than 6 years of age.

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	4/30/2012
	Study/Clinical trial Completion Date:	3/31/2014
	Final Report Submission Date:	9/30/2014
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Pediatric study was deferred because the adult and adolescent program was completed and ready for approval. The adult and adolescent program provided adequate safety data to support studies in pediatric patients < 12 years of age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Pediatric study to evaluate the safety and pharmacokinetics of Astepro Nasal Spray in children 6 months to < 6 years of age with perennial and/or seasonal allergic rhinitis

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical trial in patients 6 months to < 6 years of age

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA for the treatment of perennial and/or seasonal allergic rhinitis in pediatric patients ages 6 years to less than 12 years of age.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	09/30/2012
Study/Clinical trial Completion Date:	11/31/2013
Final Report Submission Date:	04/30/2014
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Pediatric study was deferred because the adult and adolescent program was completed and ready for approval. The adult and adolescent program provided adequate safety data to support studies in pediatric patients < 12 years of age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Evaluate the safety and efficacy of Astepro Nasal Spray in patients 6 years to < 12 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Clinical trial in patients 6 years to < 12 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Deferred pediatric study under PREA for the treatment of perennial and/or seasonal allergic rhinitis in pediatric patients ages 6 years to less than 12 years of age.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	09/30/2012
Study/Clinical trial Completion Date:	11/31/2013
Final Report Submission Date:	04/30/2014
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   Pediatric study was deferred because the adult and adolescent program was completed and ready for approval. The adult and adolescent program provided adequate safety data to support studies in pediatric patients < 12 years of age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

   Evaluate the pharmacokinetics of Astepro Nasal Spray in patients 6 years to < 12 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Pharmacokinetic trial in patients 6 years to < 12 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22371	ORIG 1	MEDA PHARMACEUTICALS INC	AZELASTINE HYDROCHLORIDE NASAL SPRAY

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
08/31/2009
PMR/PMC Development Template

Jackson, Colette

From: Greeley, George
Sent: Friday, August 28, 2009 10:39 AM
To: Jackson, Colette
Cc: Stowe, Ginneh D.; Limb, Susan; Seymour, Sally
Subject: NDA 22-371 (b) (4) - Update

Importance: High

Hi Colette,

The (b) (4) (azelastine hydrochloride 0.15%) partial waiver/deferral/plan/assessment was reviewed by the PeRC PREA Subcommittee on April 29, 2009.

The Division recommended a partial waiver for the SAR indication for pediatric patients 0-2 years because the disease/condition does not exist in children and a deferral from 2<5 years under an existing deferral using an already approved formulation. The assessment for this product includes pediatric patients 5-16 years of age.

The Division recommended a partial waiver for the PAR indication for pediatric patients 0-6 months because the disease/condition does not exist in children and a deferral from 6 months - 11 years because the product is ready for approval in adults. The assessment for this product includes pediatric patients 12-16 years of age.

The PeRC agreed with the Division to grant the partial waivers and deferrals as well as the assessments for this product.

addition, the PeRC recommends ensuring that PK studies be done prior to conducting clinical trials and that the sponsor also understand that the Division would like to include the younger age population in the studies. Both plans are missing the final report dates and it is also requested that the sponsor conduct a studies breakdown between the age groups which should be done sequentially

Addendum - August 20, 2009

The Review Division has submitted an addendum to modify the PMR for the SAR indication agreed to by the PeRC on April 29, 2009. This modification would expand the age range from 2<5 years for the deferral to now include pediatric patients 2<12 years of age.

The PeRC agreed with the Division's request to modify the PMR and grant a deferral from 2<12 years for the SAR indication.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 26, 2009

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-564-2377	**Fax number:** 301-796-9718
Phone number: 973-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371 FDA Proposed Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-371
azelastine hydrochloride 0.15% nasal spray

Please refer to your August 1, 2008, new drug application (NDA) for azelastine hydrochloride 0.15% nasal spray. We acknowledge your submission dated August 17, 2009. We have the following preliminary labeling comments. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the revisions shown in the attached labeling and described below by COB August 28, 2009.

1. Table 3 displays data values generated from the Agency's statistical analyses as discussed during the teleconference on August 21, 2009.

2. Section 14.1 and Tables 3 and Table 4 have been modified to include the results of Study MP439.

3. The Clinical Studies section has been revised to clarify the primary efficacy endpoint and the supportive secondary endpoints.

4. The Clinical Studies section has been revised to clarify the treatment arms for Studies MP433 and MP438.

5. Minor formatting changes have been made to Tables 3, 4, and 5 to ensure consistency.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosure: FDA Proposed Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ASTEPRO® Nasal Spray safely and effectively. See full prescribing information for ASTEPRO Nasal Spray.

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.1%
ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15%

Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------
ASTEPRO Nasal Spray is an H_1 receptor antagonist indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older. (1.1)

----------DOSAGE AND ADMINISTRATION---------
For intranasal use only (2.3).

Seasonal allergic rhinitis:
- ASTEPRO Nasal Spray 0.1% and 0.15%: 1 or 2 sprays per nostril twice daily in adults and adolescents 12 years of age and older (2.1)
- ASTEPRO Nasal Spray 0.15%: 2 sprays per nostril once daily in adults and adolescents 12 years of age and older (2.1)

Perennial allergic rhinitis:
- ASTEPRO Nasal Spray 0.15%: 2 sprays per nostril twice daily in adults and adolescents 12 years of age and older (2.2)

• Prime ASTEPRO Nasal Spray before initial use and when it has not been used for 3 or more days. (2.3)

----------DOSAGE FORMS AND STRENGTHS-------
ASTEPRO Nasal Spray 0.1%: 137 mcg of azelastine hydrochloride in each 0.137 mL spray (3).
ASTEPRO Nasal Spray 0.15%: 205.5 mcg of azelastine hydrochloride in each 0.137 mL spray (3).

----------CONTRAINDICATIONS----------
None.

----------WARNINGS AND PRECAUTIONS----------
• Somnolence may occur. Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking ASTEPRO Nasal Spray (5.1)
• Avoid concurrent use of alcohol or other central nervous system (CNS) depressants with ASTEPRO Nasal Spray because further decreased alertness and impairment of CNS performance may occur (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥2% incidence) are: bitter taste, nasal discomfort, epistaxis, headache, fatigue, somnolence and sneezing (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MEDA Pharmaceuticals Inc. at 1-800-526-3840 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------
• Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

revised mm/yy

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Allergic Rhinitis

ASTEPRO Nasal Spray 0.1% and 0.15% is indicated for the relief of the symptoms of seasonal and perennial allergic rhinitis in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Seasonal Allergic Rhinitis

The recommended dose of ASTEPRO Nasal Spray 0.1% and 0.15% is 1 or 2 sprays per nostril twice daily for seasonal allergic rhinitis. ASTEPRO Nasal Spray 0.15% may also be administered as 2 sprays per nostril once daily.

2.2 Perennial Allergic Rhinitis

The recommended dose of ASTEPRO Nasal Spray 0.15% for perennial allergic rhinitis is 2 sprays per nostril twice daily.

2.3 Important Administration Instructions

Administer ASTEPRO Nasal Spray by the intranasal route only.

Priming: Prime ASTEPRO Nasal Spray before initial use by releasing 6 sprays or until a fine mist appears. When ASTEPRO Nasal Spray has not been used for 3 or more days, reprime with 2 sprays or until a fine mist appears. Avoid spraying ASTEPRO Nasal Spray into the eyes.

3 DOSAGE FORMS AND STRENGTHS

ASTEPRO Nasal Spray is a nasal spray solution. Each spray of ASTEPRO Nasal Spray 0.1% delivers a volume of 0.137 mL solution containing 137 mcg of azelastine hydrochloride. Each spray of ASTEPRO Nasal Spray 0.15% delivers a volume of 0.137 mL solution containing 205.5 mcg of azelastine hydrochloride.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Activities Requiring Mental Alertness

In clinical trials, the occurrence of somnolence has been reported in some patients taking ASTEPRO Nasal Spray [*see Adverse Reactions (6.1)*]. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as operating machinery or driving a motor vehicle after administration of ASTEPRO Nasal Spray. Concurrent use of ASTEPRO Nasal Spray with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur [*see Drug Interactions (7.1)*].

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6 ADVERSE REACTIONS

Use of ASTEPRO Nasal Spray has been associated with somnolence [*see Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

ASTEPRO Nasal Spray 0.1%

The safety data described below reflect exposure to ASTEPRO Nasal Spray 0.1% in 713 patients 12 years of age and older from 2 clinical trials of 2 weeks to 12 months duration. In a 2 week, double-blind, placebo-controlled, and active controlled (Astelin® Nasal Spray; azelastine hydrochloride) clinical trial, 285 patients (115 males and 170 females) 12 years of age and older with seasonal allergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% one or two sprays per nostril daily. In the 12 month open-label, active controlled (Astelin Nasal Spray) clinical trial, 428 patients (207 males and 221 females) 12 years of age and older with perennial allergic rhinitis and/or nonallergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% two sprays per nostril twice daily. The racial and ethnic distribution for the 2 clinical trials was 82% white, 8% black, 6% Hispanic, 3% Asian, and <1% other.

Adults and Adolescents 12 Years of Age and Older

In the two week clinical trial, 835 patients 12 years of age and older with seasonal allergic rhinitis were treated with one of six treatments: one spray per nostril of either ASTEPRO Nasal Spray 0.1%, Astelin Nasal Spray or placebo twice daily; or 2 sprays per nostril of ASTEPRO Nasal Spray 0.1%, Astelin Nasal Spray, or placebo twice daily. Overall, adverse reactions were more common in the ASTEPRO Nasal Spray 0.1% treatment groups (21-28%) than in the placebo groups (16-20%). Overall, less than 1% of patients discontinued due to adverse reactions and withdrawal due to adverse reactions was similar among the treatment groups.

Table 1 contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in patients treated with ASTEPRO Nasal Spray 0.1% in the controlled clinical trial described above.

Table 1. Adverse Reactions Reported in ≥2% Patients in a 2 Week Controlled Trial in Adult and Adolescent Patients with Seasonal Allergic Rhinitis

	1 spray twice daily			2 sprays twice daily		
	ASTEPRO Nasal Spray 0.1% (N=139)	Astelin Nasal Spray (N=137)	Vehicle Placebo (N=137)	ASTEPRO Nasal Spray 0.1% (N=146)	Astelin Nasal Spray (N=137)	Vehicle Placebo (N=138)
Bitter Taste	8 (6%)	13 (10%)	2 (2%)	10 (7%)	11 (8%)	3 (2%)
Epistaxis	3 (2%)	8 (6%)	3 (2%)	4 (3%)	3 (2%)	0 (0%)
Headache	2 (1%)	5 (4%)	1 (<1%)	4 (3%)	3 (2%)	1 (<1%)
Nasal Discomfort	0 (0%)	3 (2%)	1 (<1%)	2 (1%)	6 (4%)	0 (0%)
Fatigue	0 (0%)	1 (<1%)	1 (<1%)	3 (2%)	3 (2%)	1 (<1%)
Somnolence	2 (1%)	2 (2%)	0 (0%)	3 (2%)	2 (1%)	0 (0%)

Long-Term (12 Month) Safety Trial:

In the 12 month, open-label, active-controlled, long-term safety trial, 862 patients 12 years of age and older with perennial allergic and/or nonallergic rhinitis were treated with ASTEPRO Nasal Spray 0.1% two sprays per nostril twice daily or Astelin Nasal Spray two sprays per nostril twice daily. The most frequently reported adverse reactions were headache, bitter taste, epistaxis, and nasopharyngitis and were generally similar between

treatment groups. Focused nasal examinations were performed and showed that the incidence of nasal mucosal ulceration in each treatment group was approximately 1% at baseline and approximately 1.5% throughout the 12 month treatment period. In each treatment group, 5-7% of patients had mild epistaxis. No patients had reports of nasal septal perforation or severe epistaxis. Twenty-two patients (5%) treated with ASTEPRO Nasal Spray 0.1% and 17 patients (4%) treated with Astelin Nasal Spray discontinued from the trial due to adverse events.

ASTEPRO Nasal Spray 0.15%

The safety data described below reflect exposure to ASTEPRO Nasal Spray 0.15% in 2010 patients (12 years of age and older) with seasonal or perennial allergic rhinitis from 8 clinical trials of 2 weeks to 12 months duration. In 7 double-blind, placebo-controlled clinical trials of 2 to 4 weeks duration, 1544 patients (560 males and 984 females) with seasonal or perennial allergic rhinitis were treated with ASTEPRO Nasal Spray 0.15% two sprays per nostril once or twice daily. In the 12 month open-label, active controlled clinical trial, 466 patients (156 males and 310 females) with perennial allergic rhinitis were treated with ASTEPRO Nasal Spray 0.15% two sprays per nostril twice daily. Of these 466 patients, 153 had participated in the 4-week placebo-controlled perennial allergic rhinitis clinical trials. The racial distribution for the 8 clinical trials was 80% white, 13% black, 2% Asian, and 5% other.

Adults and Adolescents 12 Years of Age and Older

In the 7 placebo controlled clinical trials of 2 to 4 week duration, 2343 patients with seasonal allergic rhinitis and 540 patients with perennial allergic rhinitis were treated with two sprays per nostril of either ASTEPRO Nasal Spray 0.15% or placebo once or twice daily. Overall, adverse reactions were more common in the ASTEPRO Nasal Spray 0.15% treatment groups (16-31%) than in the placebo groups (11-24%). Overall, less than 2% of patients discontinued due to adverse reactions and withdrawal due to adverse reactions was similar among the treatment groups.

Table 2 contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in patients treated with ASTEPRO Nasal Spray 0.15% in the seasonal and perennial allergic rhinitis controlled clinical trials.

Table 2. Adverse Reactions with ≥2% Incidence in Placebo-Controlled Trials of 2 to 4 Weeks' Duration with ASTEPRO Nasal Spray 0.15% in Adult and Adolescent Patients With Seasonal or Perennial Allergic Rhinitis

	2 sprays twice daily		2 sprays once daily	
	ASTEPRO Nasal Spray 0.15% (N=523)	Vehicle Placebo (N=523)	ASTEPRO Nasal Spray 0.15% (N=1021)	Vehicle Placebo (N=816)
Bitter Taste	31 (6%)	5 (1%)	38 (4%)	2 (<1%)
Nasal Discomfort	18 (3%)	12 (2%)	37 (4%)	7 (1%)
Epistaxis	5 (1%)	7 (1%)	21 (2%)	14 (2%)
Sneezing	9 (2%)	1 (<1%)	14 (1%)	0 (0%)

In the above trials, somnolence was reported in <1% of patients treated with ASTEPRO Nasal Spray 0.15% (11 of 1544) or vehicle placebo (1 of 1339).

Long-Term (12 Month) Safety Trial:

In the 12 month, open-label, active-controlled, long-term safety trial, 466 patients (12 years of age and older) with perennial allergic rhinitis were treated with ASTEPRO Nasal Spray 0.15% two sprays per nostril twice daily and 237 patients were treated with mometasone nasal spray two sprays per nostril once daily. The most frequently reported adverse reactions (>5%) with ASTEPRO Nasal Spray 0.15% were bitter taste, headache, sinusitis, and epistaxis. Focused nasal examinations were performed and no nasal ulcerations or septal perforations were observed. In each treatment group, approximately 3% of patients had mild epistaxis. No patients had reports of severe epistaxis. Fifty-four patients (12%) treated with ASTEPRO Nasal Spray 0.15% and 17 patients (7%) treated with mometasone nasal spray discontinued from the trial due to adverse events.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the post approval use of the Astelin brand of azelastine hydrochloride 0.1% nasal spray (total daily dose 0.55 mg to 1.1 mg). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure. Adverse reactions reported include the following: anaphylactoid reaction, application site irritation, atrial fibrillation, blurred vision, chest pain, confusion, dizziness, dyspnea, facial edema, hypertension, involuntary muscle contractions, nervousness, palpitations, paresthesia, parosmia, paroxysmal sneezing, pruritus, rash, disturbance or loss of sense of smell and/or taste, tachycardia, tolerance, urinary retention, and xerophthalmia.

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

Concurrent use of ASTEPRO Nasal Spray with alcohol or other central nervous system depressants should be avoided because reductions in alertness and impairment of central nervous system performance may occur [*see Warnings and Precautions (5.1)*].

7.2 Erythromycin and Ketoconazole

Interaction studies investigating the cardiac effects, as measured by the corrected QT interval (QTc), of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. Oral erythromycin (500 mg three times daily for 7 days) had no effect on azelastine pharmacokinetics or QTc based on analyses of serial electrocardiograms. Ketoconazole (200 mg twice daily for 7 days) interfered with the measurement of azelastine plasma concentrations on the analytic HPLC; however, no effects on QTc were observed [*see Clinical Pharmacology (12.2) and (12.3)*].

7.3 Cimetidine

Cimetidine (400 mg twice daily) increased the mean C_{max} and AUC of orally administered azelastine hydrochloride (4 mg twice daily) by approximately 65% [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled clinical trials in pregnant women. Azelastine hydrochloride has been shown to cause developmental

toxicity in mice, rats, and rabbits. ASTEPRO Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects: In mice, azelastine hydrochloride caused embryo-fetal death, malformations (cleft palate; short or absent tail; fused, absent or branched ribs), delayed ossification, and decreased fetal weight at an oral dose approximately 170 times the maximum recommended human daily intranasal dose (MRHDID) in adults on a mg/m^2 basis. This dose also caused maternal toxicity as evidenced by decreased body weight. Neither fetal nor maternal effects occurred at a dose that was approximately 7 times the MRHDID.

In rats, azelastine hydrochloride caused malformations (oligo- and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity, at an oral dose approximately 150 times the MRHDID in adults on a mg/m^2 basis. At a dose approximately 340 times the MRHDID, azelastine hydrochloride also caused embryo-fetal death and decreased fetal weight; however, this dose caused severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose approximately 15 times the MRHDID.

In rabbits, azelastine hydrochloride caused abortion, delayed ossification and decreased fetal weight at oral doses approximately 300 times the MRHDID in adults on a mg/m^2 basis; however, these doses also resulted in severe maternal toxicity. Neither fetal nor maternal effects occurred at a dose approximately 3 times the MRHDID.

8.3 Nursing Mothers

It is not known whether azelastine hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ASTEPRO Nasal Spray is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ASTEPRO Nasal Spray in pediatric patients below the age of 12 years have not been established.

8.5 Geriatric Use

Clinical trials of ASTEPRO Nasal Spray did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

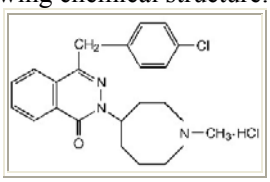
There have been no reported overdosages with ASTEPRO Nasal Spray. Acute overdosage by adults with this dosage form is unlikely to result in clinically significant adverse events, other than increased somnolence, since one 30-mL bottle of ASTEPRO Nasal Spray 0.1% contains up to 30 mg of azelastine hydrochloride and one 30-mL bottle ASTEPRO Nasal Spray 0.15% contains up to 45 mg of azelastine hydrochloride. Clinical trials in adults with single doses of the oral formulation of azelastine hydrochloride (up to 16 mg) have not resulted in increased incidence of serious adverse events. General supportive measures should be employed if overdosage occurs. There is no known antidote to ASTEPRO Nasal Spray. Oral ingestion of antihistamines has the potential to

cause serious adverse effects in children. Accordingly, ASTEPRO Nasal Spray should be kept out of the reach of children. Oral doses of 120 mg/kg and greater (approximately 300 times the maximum recommended human daily intranasal dose [MRHDID] in adults and children on a mg/m^2 basis) were lethal in mice. Responses seen prior to death were tremor, convulsions, decreased muscle tone, and salivation. In dogs, single oral doses as high as 10 mg/kg (approximately 160 times the MRHDID in adults and children on a mg/m^2 basis) were well tolerated, but single oral doses of 20 mg/kg were lethal.

11 DESCRIPTION

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.1%, 137 micrograms (mcg), is an antihistamine formulated as a metered-spray solution for intranasal administration. ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15%, 205.5 micrograms (mcg), is formulated as a metered-spray solution for intranasal administration.

Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is $C_{22}H_{24}ClN_3O \cdot HCl$ with the following chemical structure:



ASTEPRO Nasal Spray 0.1% contains 0.1% azelastine hydrochloride in an isotonic aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride (125 mcg/mL), and purified water (pH 6.4).

After priming [*see Dosage and Administration (2.3)*], each metered spray delivers a 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base). The 30-mL (net weight 30 gm of solution) bottle provides 200 metered sprays.

ASTEPRO Nasal Spray 0.15% contains 0.15% azelastine hydrochloride in an isotonic aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride (125 mcg/mL), and purified water (pH 6.4).

After priming [*see Dosage and Administration (2.3)*], each metered spray delivers a 0.137 mL mean volume containing 205.5 mcg of azelastine hydrochloride (equivalent to 187.6 mcg of azelastine base). The 17 mL (net weight 17 gm of solution) bottle provides 106 metered sprays and the 30 mL (net weight 30 gm of solution) bottle provides 200 metered sprays.

12 CLINCIAL PHARMACOLOGY

12.1 Mechanism of Action

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H_1-receptor antagonist activity in isolated tissues, animal models, and humans. ASTEPRO Nasal Spray is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in *in vitro* studies. The major metabolite, desmethylazelastine, also possesses H_1-receptor antagonist activity.

12.2 Pharmacodynamics

Cardiac Effects:

In a placebo-controlled trial (95 patients with allergic rhinitis), there was no evidence of an effect of azelastine hydrochloride nasal spray (2 sprays per nostril twice daily for 56 days) on cardiac repolarization as represented by the corrected QT interval (QTc) of the electrocardiogram. 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.

Interaction studies investigating the cardiac repolarization effects of concomitantly administered oral azelastine hydrochloride and erythromycin or ketoconazole were conducted. Oral erythromycin had no effect on azelastine pharmacokinetics or QTc based on analysis of serial electrocardiograms. Ketoconazole interfered with the measurement of azelastine plasma levels; however, no effects on QTc were observed [*see Drug Interactions (7.2)*].

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12.3 Pharmacokinetics

Absorption: After intranasal administration of 2 sprays per nostril (548 mcg total dose) of ASTEPRO Nasal Spray 0.1%, the mean azelastine peak plasma concentration (C_{max}) is 200 pg/mL, the mean extent of systemic exposure (AUC) is 5122 pg•hr/mL and the median time to reach C_{max} (t_{max}) is 3 hours. After intranasal administration of 2 sprays per nostril (822 mcg total dose) of ASTEPRO Nasal Spray 0.15%, the mean azelastine peak plasma concentration (C_{max}) is 409 pg/mL, the mean extent of systemic exposure (AUC) is 9312 pg•hr/mL and the median time to reach C_{max} (t_{max}) is 4 hours. The systemic bioavailability of azelastine hydrochloride is approximately 40% after intranasal administration.

Distribution: Based on intravenous and oral administration, the steady-state volume of distribution of azelastine is 14.5 L/kg. In vitro studies with human plasma indicate that the plasma protein binding of azelastine and its metabolite, desmethylazelastine, are approximately 88% and 97%, respectively.

Metabolism: Azelastine is oxidatively metabolized to the principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system. The specific P450 isoforms responsible for the biotransformation of azelastine have not been identified. After a single-dose, intranasal administration of ASTEPRO Nasal Spray 0.1% (548 mcg total dose), the mean desmethylazelastine C_{max} is 23 pg/mL, the AUC is 2131 pg•hr/mL and the median t_{max} is 24 hours. After a single-dose, intranasal administration of ASTEPRO Nasal Spray 0.15% (822 mcg total dose), the mean desmethylazelastine C_{max} is 38 pg/mL, the AUC is 3824 pg•hr/mL and the median t_{max} is 24 hours. After intranasal dosing of azelastine to steady-state, plasma concentrations of desmethylazelastine range from 20-50% of azelastine concentrations.

Elimination: Following intranasal administration of ASTEPRO Nasal Spray 0.1%, the elimination half-life of azelastine is 22 hours while that of desmethylazelastine is 52 hours. Following intranasal administration of ASTEPRO Nasal Spray 0.15%, the elimination half-life of azelastine is 25 hours while that of desmethylazelastine is 57

hours. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted in the feces with less than 10% as unchanged azelastine.

Special Populations:

Hepatic Impairment: Following oral administration, pharmacokinetic parameters were not influenced by hepatic impairment.

Renal Impairment: Based on oral, single-dose studies, renal insufficiency (creatinine clearance <50 mL/min) resulted in a 70-75% higher C_{max} and AUC compared to healthy subjects. Time to maximum concentration was unchanged.

Age: Following oral administration, pharmacokinetic parameters were not influenced by age.

Gender: Following oral administration, pharmacokinetic parameters were not influenced by gender.

Race: The effect of race has not been evaluated.

Drug-Drug Interactions:

Erythromycin: Co-administration of orally administered azelastine (4 mg twice daily) with erythromycin (500 mg three times daily for 7 days) resulted in C_{max} of 5.36 ± 2.6 ng/mL and AUC of 49.7 ± 24 ng•h/mL for azelastine, whereas, administration of azelastine alone resulted in C_{max} of 5.57 ± 2.7 ng/mL and AUC of 48.4 ± 24 ng•h/mL for azelastine [see *Drug Interactions* (*7.2)*].

Cimetidine and Ranitidine: In a multiple-dose, steady-state drug interaction trial in healthy subjects, cimetidine (400 mg twice daily) increased orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%. Co-administration of orally administered azelastine (4 mg twice daily) with ranitidine hydrochloride (150 mg twice daily) resulted in C_{max} of 8.89 ±3.28 ng/mL and AUC of 88.22 ± 40.43 ng•h/mL for azelastine, whereas, administration of azelastine alone resulted in C_{max} of 7.83 ± 4.06 ng/mL and AUC of 80.09 ± 43.55 ng•h/mL for azelastine [see *Drug Interactions* (*7.3*)].

Theophylline: No significant pharmacokinetic interaction was observed with the co-administration of an oral 4 mg dose of azelastine hydrochloride twice daily and theophylline 300 mg or 400 mg twice daily.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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. These doses were approximately 150 and 60 times the maximum recommended human daily intranasal dose [MRHDID] on a mg/m^2 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 150 times the MRHDID in adults on a mg/m^2 basis). At 68.6 mg/kg (approximately 340 times the MRHDID on a mg/m^2 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.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Azelastine hydrochloride has been shown to cause developmental toxicity. Treatment of mice with an oral dose of 68.6 mg/kg (approximately 170 times the maximum recommended human daily intranasal dose [MRHDID] on a mg/m^2 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 7 times the MRHDID on a mg/m^2 basis).

In rats, an oral dose of 30 mg/kg (approximately 150 times the MRHDID on a mg/m^2 basis) caused malformations (oligo-and brachydactylia), delayed ossification and skeletal variations, in the absence of maternal toxicity. At 68.6 mg/kg (approximately 340 times the MRHDID on a mg/m^2 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 15 times the MRHDID on a mg/m^2 basis).

In rabbits, oral doses of 30 mg/kg and greater (approximately 300 times the MRHDID on a mg/m^2 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 3 times the MRHDID on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Seasonal Allergic Rhinitis

ASTEPRO Nasal Spray 0.1%

The efficacy and safety of ASTEPRO Nasal Spray 0.1% was evaluated in a 2 week, randomized, multicenter, double-blind, placebo-controlled clinical trial including 834 adult and adolescent patients 12 years of age and older with symptoms of seasonal allergic rhinitis. The population was 12 to 83 years of age (60% female, 40% male; 69% white, 16% black, 12% Hispanic, 2% Asian, 1% other).

Patients were randomized to one of six treatment groups: 1 spray per nostril of either ASTEPRO Nasal Spray 0.1%, Astelin (azelastine hydrochloride) Nasal Spray or vehicle placebo twice daily; or 2 sprays per nostril of ASTEPRO Nasal Spray 0.1%, Astelin (azelastine hydrochloride) Nasal Spray or vehicle placebo twice daily.

Assessment of efficacy was based on the 12-hour reflective total nasal symptom score (rTNSS) assessed daily in the morning and evening, in addition to the instantaneous total nasal symptom score (iTNSS) and other supportive secondary efficacy variables. TNSS is calculated as the sum of the patients' scoring of the four individual nasal symptoms (rhinorrhea, nasal congestion, sneezing, and nasal itching) on a 0 to 3 categorical severity scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe). The rTNSS required patients to record symptom severity over the previous 12 hours. For the primary efficacy endpoint, the mean change from baseline rTNSS, morning (AM) and evening (PM) rTNSS scores were summed for each day (maximum score of 24) and then averaged over the 2 weeks. The iTNSS, recorded immediately prior to the next dose, were assessed as an indication of whether the effect was maintained over the dosing interval.

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In this trial, ASTEPRO Nasal Spray 0.1% two sprays twice a day demonstrated a greater decrease in rTNSS and iTNSS than placebo and the difference was statistically significant. The trial results are presented in Table 3 (Trial 1).

The efficacy of ASTEPRO Nasal Spray 0.1% one spray per nostril twice daily for seasonal allergic rhinitis is supported by two, 2-week, placebo controlled clinical trials with Astelin (azelastine hydrochloride) Nasal Spray in 413 patients with seasonal allergic rhinitis. In these trials, efficacy was assessed using the TNSS (described above). Astelin Nasal Spray demonstrated a greater decrease from baseline in the summed AM and PM rTNSS compared with placebo and the difference was statistically significant.

ASTEPRO Nasal Spray 0.15%

The efficacy and safety of ASTEPRO Nasal Spray 0.15% in seasonal allergic rhinitis was evaluated in five randomized, multicenter, double-blind, placebo-controlled clinical trials in 1544 adult and adolescent patients 12 years and older with symptoms of seasonal allergic rhinitis (Trials 2, 3, 4, 5, and 6). The population of the trials was 12 to 83 years of age (64% female, 36% male; 81% white, 12% black, <2% Asian, 5% other; 23% Hispanic, 77% non-Hispanic). Assessment of efficacy was based on the rTNSS, iTNSS as described above, and other supportive secondary efficacy variables. The primary efficacy endpoint was the mean change from baseline in rTNSS over 2 weeks.

Two 2-week seasonal allergic rhinitis trials evaluated the efficacy of ASTEPRO Nasal Spray 0.15% dosed at 2 sprays twice daily. The first trial (Trial 2) compared the efficacy of ASTEPRO Nasal Spray 0.15% and Astelin (azelastine hydrochloride) Nasal Spray to vehicle placebo. The other trial (Trial 3) compared the efficacy of ASTEPRO Nasal Spray 0.15% and ASTEPRO Nasal Spray 0.1% to vehicle placebo. In these two trials, ASTEPRO Nasal Spray 0.15% demonstrated greater decreases in rTNSS than placebo and the differences were statistically significant (Table 3).

Three 2-week seasonal allergic rhinitis trials evaluated the efficacy of ASTEPRO Nasal Spray 0.15% dosed at 2 sprays once daily compared to vehicle placebo. Trial 4 demonstrated a greater decrease in rTNSS than placebo and the difference was statistically significant (Table 3). Trial 5 and Trial 6 were conducted in patients with Texas mountain cedar allergy. In Trial 5 and Trial 6, ASTEPRO Nasal Spray 0.15% demonstrated a greater decrease in rTNSS than placebo and the differences were statistically significant (Trials 5 and 6; Table 3). Instantaneous TNSS results for the once daily dosing regimen of ASTEPRO Nasal Spray 0.15% are shown in Table 4. In Trials 5 and 6, ASTEPRO Nasal Spray 0.15% demonstrated a greater decrease in iTNSS than placebo and the differences were statistically significant.

Table 3. Mean Change from Baseline in Reflective TNSS over 2 Weeks* in Adults and Children ≥ 12 years with Seasonal Allergic Rhinitis

	Treatment (sprays per nostril)	n	Baseline LS Mean	Change from Baseline	Difference From Placebo		
					LS Mean	95% CI	P value
Trial 1							
Two sprays twice daily	ASTEPRO Nasal Spray 0.1%	146	18.0	-5.0	-2.2	-3.2,-1.2	<0.001
	Astelin Nasal Spray	137	18.2	-4.2	-1.4	-2.4,-0.4	0.01
	Vehicle Placebo	138	18.2	-2.8			
One spray twice daily	ASTEPRO Nasal Spray 0.1%	139	18.2	-4.2	-0.7	-1.7, 0.3	0.18
	Astelin Nasal Spray	137	18.1	-4.0	-0.4	-1.5, 0.6	0.41
	Vehicle Placebo	137	18.0	-3.5			
Trial 2							

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Two sprays twice daily	ASTEPRO Nasal Spray 0.15%	153	18.2	-4.3	-1.2	-2.1, -0.3	0.01
	Astelin Nasal Spray	153	17.9	-3.9	-0.9	-1.8, 0.1	0.07
	Vehicle Placebo	153	18.1	-3.0			
Trial 3							
Two sprays twice daily	ASTEPRO Nasal Spray 0.15%	177	17.7	-5.1	-3.0	-3.9, -2.1	<0.001
	ASTEPRO Nasal Spray 0.1%	169	18.2	-4.2	-2.1	-3.0, -1.2	<0.001
	Vehicle Placebo	177	17.7	-2.1			
Trial 4							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	238	17.4	-3.4	-1.0	-1.7, -0.3	0.008
	Vehicle Placebo	242	`7.4	-2.4			
Trial 5							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	266	18.5	-3.3	-1.4	-2.1, -0.8	<0.001
	Vehicle Placebo	266	18.0	-1.9			
Trial6							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	251	18.5	-3.4	-1.4	-2.1, -0.7	<0.001
	Vehicle Placebo	254	18.8	-2.0			
*Sum of AM and PM rTNSS for each day (Maximum score=24) and averaged over the 14 day treatment period							

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Table 4. Mean Change from Baseline AM Instantaneous TNSS over 2 Weeks* in Adults and Children ≥ 12 years with Seasonal Allergic Rhinitis

Treatment (sprays per nostril once daily)		n	Baseline LS Mean	Change from Baseline	Difference From Placebo		
					LS Mean	95% CI	P value
Trial 4							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	238	8.1	-1.3	-0.2	-0.6, 0.1	0.15
	Vehicle Placebo	242	8.3	-1.1			
Trial 5							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	266	8.7	-1.4	-0.7	-1.0, -0.4	<0.001
	Vehicle Placebo	266	8.3	-0.7			
Trial 6							
Two sprays once daily	ASTEPRO Nasal Spray 0.15%	251	8.9	-1.4	-0.6	-0.9, -0.3	<0.001
	Vehicle Placebo	254	8.9	-0.8			

*AM iTNSS for each day (Maximum score=12) and averaged over the 14 day treatment period

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ASTEPRO Nasal Spray 0.15% at a dose of 1 spray twice daily was not studied. The ASTEPRO Nasal Spray 0.15% 1 spray twice daily dosing regimen is supported by previous findings of efficacy for Astelin (azelastine hydrochloride) Nasal Spray and a favorable comparison of ASTEPRO Nasal Spray 0.15% to Astelin Nasal Spray and ASTEPRO Nasal Spray 0.1% (Table 3).

Deleted: The efficacy of ASTEPRO Nasal Spray one spray per nostril twice daily for seasonal allergic rhinitis is supported by two, 2-week, placebo controlled clinical trials with Astelin Nasal Spray in 413 patients with seasonal allergic rhinitis. In these trials, efficacy was assessed using the TNSS (described above). Astelin Nasal Spray demonstrated a greater decrease from baseline in the summed AM and PM rTNSS compared with placebo and the difference was statistically significant.

14.2 Perennial Allergic Rhinitis

ASTEPRO Nasal Spray 0.15%

The efficacy and safety of ASTEPRO Nasal Spray 0.15% in perennial allergic rhinitis was evaluated in one randomized, multicenter, double-blind, placebo-controlled clinical trial in adult and adolescent patients 12 years and older with symptoms of perennial allergic rhinitis. The population of the trial was 12 to 84 years of age (68% female, 32% male; 85% white, 11% black, 1% Asian, 3% other; 17% Hispanic, 83% non-Hispanic).

Assessment of efficacy was based on the 12-hour reflective total nasal symptom score (rTNSS) assessed daily in the morning and evening, the instantaneous total nasal symptom score (iTNSS), and other supportive secondary efficacy variables. The primary efficacy endpoint was the mean change from baseline rTNSS over 4 weeks. The one 4-week perennial allergic rhinitis trial evaluated the efficacy of ASTEPRO Nasal Spray 0.15%, ASTEPRO Nasal Spray 0.1%, and vehicle placebo dosed at 2 sprays per nostril twice daily. In this trial, ASTEPRO Nasal Spray 0.15% demonstrated a greater decrease in rTNSS than placebo and the difference was statistically significant (Table 5).

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Table 5. Mean Change from Baseline in Reflective TNSS over 4 Weeks* In Adults and Children ≥ 12 years with Perennial Allergic Rhinitis

Treatment (sprays per nostril twice daily)		n	Baseline LS Mean	Change from Baseline	Difference From Placebo		
					LS Mean	95% CI	P value
Two Sprays twice daily	ASTEPRO Nasal Spray 0.15%	192	15.8	-4.0	-0.9	-1.7, -0.1	0.03
	ASTEPRO Nasal Spray 0.1%	194	15.5	-3.8	-0.7	-1.5, 0.1	0.08
	Placebo Vehicle	192	14.7	-3.1			

*Sum of AM and PM rTNSS for each day (Maximum score=24) and averaged over the 28 day treatment period

16 HOW SUPPLIED/STORAGE AND HANDLING

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.1% (NDC 0037-0242-30) is supplied as a 30 mL package delivering 200 metered sprays in a high-density polyethylene (HDPE) bottle fitted with a metered-dose spray pump unit. The spray pump unit consists of a nasal spray pump fitted with a blue safety clip and a blue plastic dust cover. The net content of the bottle is 30 mL (net weight 30 gm of solution). Each bottle contains 30 mg (1 mg/mL) of azelastine hydrochloride. After priming [*see Dosage and Administration (2.3)*], each spray delivers a fine mist containing a mean volume of 0.137 mL solution containing 137 mcg of azelastine hydrochloride. The correct amount of medication in each spray cannot be assured before the initial priming and after 200 sprays have been used, even though the bottle is not completely empty. The bottle should be discarded after 200 sprays have been used.

ASTEPRO (azelastine hydrochloride) Nasal Spray 0.15% is supplied as a 17 mL package (NDC 0037-0243-17) delivering 106 metered sprays or as a 30 mL package (NDC 0037-0243-30) delivering 200 metered sprays in a high-density polyethylene (HDPE) bottle fitted with a metered-dose spray pump unit. The spray pump unit consists of a nasal spray pump fitted with a blue safety clip and a blue plastic dust cover. The net contents of the bottles are 17 mL (net weight 17 gm of solution) or 30 mL (net weight 30 gm of solution). The 17 ml bottle contains 25.5 mg and the 30 mL bottle contains 45 mg (1.5 mg/mL) of azelastine hydrochloride. After priming [*see Dosage and Administration (2.3)*], each spray delivers a fine mist containing a mean volume of 0.137 mL solution containing 205.5 mcg of azelastine hydrochloride. The correct amount of medication in each spray cannot be assured before the initial priming and after 106 sprays for the 17 mL bottle or 200 sprays for the 30 mL bottle have been used, even though the bottle is not completely empty. The bottle should be discarded after 106 sprays for the 17 mL bottle or 200 sprays for the 30 mL bottle have been used.

ASTEPRO Nasal Spray 0.1% and 0.15% should not be used after the expiration date "EXP" printed on the medicine label and carton.

Storage:

Store upright at controlled room temperature 20° - 25°C (68° - 77°F). Protect from freezing.

17 PATIENT COUNSELING INFORMATION

[*See FDA-Approved Patient Labeling*]

Patients should be instructed to use ASTEPRO Nasal Spray only as prescribed. For the proper use of the nasal spray and to attain maximum improvement, the patient should read and follow carefully the accompanying FDA-Approved Patient Labeling.

17.1 Activities Requiring Mental Alertness

Somnolence has been reported in some patients taking ASTEPRO Nasal Spray. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as driving or operating machinery after administration of ASTEPRO Nasal Spray [*see Warnings and Precautions (5.1)*].

17.2 Concurrent Use of Alcohol and other Central Nervous System Depressants

Concurrent use of ASTEPRO Nasal Spray with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and

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additional impairment of central nervous system performance may occur [*see Warnings and Precautions (5.1)*].

17.3 Common Adverse Reactions

Patients should be informed that the treatment with ASTEPRO Nasal Spray may lead to adverse reactions, which include bitter taste, nasal discomfort, epistaxis, headache, fatigue, somnolence, and sneezing [*see Adverse Reactions (6.1)*].

17.4 Priming

Patients should be instructed to prime the pump before initial use and when ASTEPRO Nasal Spray has not been used for 3 or more days [*see Dosage and Administration (2.3)*].

17.5 Keep Spray Out of Eyes

Patients should be instructed to avoid spraying ASTEPRO Nasal Spray into their eyes.

17.6 Keep Out of Children's Reach

Patients should be instructed to keep ASTEPRO Nasal Spray out of the reach of children. If a child accidentally ingests ASTEPRO Nasal Spray, seek medical help or call a poison control center immediately.

Manufactured by:
MEDA Pharmaceuticals
MEDA Pharmaceuticals Inc.
Somerset, NJ 08873

Astelin, ASTEPRO and MEDA Pharmaceuticals are trademarks or registered trademarks of MEDA Pharmaceuticals Inc.

PATIENT INFORMATION

ASTEPRO [*AS-ta-PRO*]
(azelastine hydrochloride)
Nasal Spray 0.1% and 0.15%

Important: For use in your nose only

Read this information carefully before you start using ASTEPRO Nasal Spray and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is ASTEPRO Nasal Spray?

- ASTEPRO Nasal Spray 0.1% and 0.15% is a prescription medicine used to relieve symptoms of seasonal allergies in people age 12 and older.
- ASTEPRO Nasal Spray 0.15% is also used to relieve symptoms of year-round allergies in people age 12 and older.
- ASTEPRO Nasal Spray contains an antihistamine that may help reduce the nasal symptoms of rhinitis (inflammation of the lining of the nose): stuffy nose, runny nose, itching and sneezing.

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It is not known if ASTEPRO Nasal Spray works and is safe or effective in children younger than age 12.

What should I tell my healthcare provider before using ASTEPRO Nasal Spray?
Before using ASTEPRO Nasal Spray tell your healthcare provider about all your medical conditions, including if you are:
• allergic to any of the ingredients in ASTEPRO Nasal Spray. See the end of this leaflet for a complete list of ingredients in ASTEPRO Nasal Spray.
• pregnant, think you may be pregnant, or planning to become pregnant. It is not known if ASTEPRO Nasal Spray will harm your unborn baby.
• breastfeeding. It is not known if ASTEPRO Nasal Spray passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal products. ASTEPRO Nasal Spray and other medicines may affect each other, causing side effects.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider when you get a new medicine.

How should I use ASTEPRO Nasal Spray?
• ASTEPRO Nasal Spray is to be sprayed in your nose only. **Do not spray it into your eyes or mouth.**
• Use ASTEPRO Nasal Spray exactly as your healthcare provider tells you. **Do not** use more than your healthcare provider tells you.
• Read the Patient Instructions for Use at the end of this leaflet for detailed instructions about how to use ASTEPRO Nasal Spray.
• Before you use ASTEPRO Nasal Spray for the first time, you will need to prime the bottle. See priming instructions at the end of this leaflet in the detailed Patient Instructions for Use.
• Do not use ASTEPRO Nasal Spray unless you see a fine mist after you do the priming sprays.
• Throw away your ASTEPRO Nasal Spray 0.1% bottle after using 200 sprays. Even though the bottle may not be completely empty, you may not get the correct dose of medicine.
• Throw away your ASTEPRO Nasal Spray 0.15% bottle after using 106 sprays (for the 17 mL bottle) or 200 sprays (for the 30 mL bottle). Even though the bottle may not be completely empty, you may not get the correct dose of medicine.

• **If a child accidentally swallows ASTEPRO Nasal Spray, get medical help or call a poison control center right away.**

What should I avoid while using ASTEPRO Nasal Spray?
ASTEPRO Nasal Spray can cause sleepiness:
• Do not drive a car, operate machinery or do dangerous activities after you use ASTEPRO Nasal Spray.

• Avoid drinking alcohol or taking other medicines that may cause you to feel sleepy while using ASTEPRO Nasal Spray.

What are the possible side effects of ASTEPRO Nasal Spray?
Side effects of ASTEPRO Nasal Spray include:
• unusual taste (bitter)
• nose pain or discomfort
• nosebleeds
• headache
• fatigue
• sleepiness
• sneezing

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of ASTEPRO Nasal Spray. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ASTEPRO Nasal Spray?
• Keep ASTEPRO Nasal Spray upright at 68° to 77°F (20° to 25°C).
• Do not freeze ASTEPRO Nasal Spray.
• Do not use ASTEPRO Nasal Spray after the expiration date "EXP" on the medicine label and box.

Keep ASTEPRO Nasal Spray and all medicines out of reach of children.

General information about ASTEPRO Nasal Spray.

Medicines are sometimes prescribed for conditions other than those mentioned in patient information leaflets. Do not use ASTEPRO Nasal Spray for a condition for which it was not prescribed. Do not give ASTEPRO Nasal Spray to other people, even if they have the same symptoms that you have. It may harm them.

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This patient information leaflet summarizes the most important information about ASTEPRO Nasal Spray. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ASTEPRO Nasal Spray that is written for health professionals.

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For more information, go to www.ASTEPRO.com or call 1-800-598-4856.

What are the ingredients in ASTEPRO Nasal Spray?
Active ingredient: azelastine hydrochloride

Inactive ingredients: sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride, and purified water.

MEDA Pharmaceuticals
MEDA Pharmaceuticals Inc.
Somerset, NJ 08873

Patient Instructions for Use

For use in your nose only

It is important that you read and follow these Patient Instructions for Use carefully to be sure you use ASTEPRO Nasal Spray the right way.

For the correct dose of medicine:

- Use ASTEPRO Nasal Spray exactly as prescribed by your healthcare provider.
- Keep your head tilted downward when spraying into your nostril.
- Change nostrils each time you use the spray.
- **Breathe gently and do not tip your head back after using the spray.** This will keep the medicine from running down into your throat. You may get a bitter taste in your mouth.

Follow the instructions below to use your ASTEPRO Nasal Spray pump.
See Figure 1.

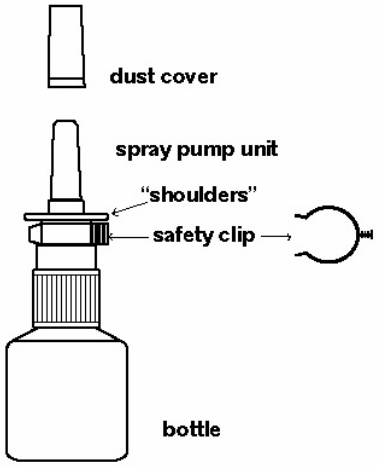

Figure 1

Before you use ASTEPRO Nasal Spray for the first time, you will need to prime the bottle.

To prime:

1. Remove the blue dust cover over the tip of the bottle and the blue safety clip just under the “shoulders” of the bottle. See Figure 2.

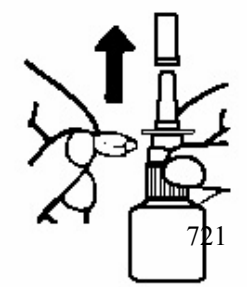

Figure 2

2. Hold the bottle upright with two fingers on the shoulders of the spray pump unit and put your thumb on the bottom of the bottle. Press upward with your thumb and release for the pumping action. Repeat this until you see a fine mist. This should happen in 6 sprays or less. See Figure 3.

   Now your pump is primed and ready to use.

Figure 3

3. To get a fine mist you must pump the spray fast and use firm pressure against the bottom of the bottle. If you see a stream of liquid, the spray will not work right and may cause nasal discomfort.

4. If you do not use ASTEPRO Nasal Spray for 3 or more days, you will need to prime the pump with 2 sprays or until you see a fine mist. If you do not see a fine mist, clean the tip of the spray nozzle. See the cleaning section below.

To Use ASTEPRO Nasal Spray:

1. Gently blow your nose to clear nostrils.
2. Keep your head tilted downward toward your toes.
3. Place the spray tip ¼ to ½ inch into one nostril. Hold bottle upright and aim the spray tip toward the back of the nose. See Figure 4.
4. Close your other nostril with a finger. Press the pump one time and sniff gently at the same time, keeping your head tilted forward and down.

Figure 4

5. Repeat in other nostril.

6. If your healthcare provider tells you to use 2 sprays in each nostril, repeat Steps 2 through 5 above for the second spray in each nostril.
7. Breathe in gently, and **do not tilt your head back** after using ASTEPRO Nasal Spray. This will help to keep the medicine from going into your throat.
8. When you finish using ASTEPRO Nasal Spray, wipe the spray tip with a clean tissue or cloth. Put the safety clip and dust cover back on the bottle.

To Clean the Spray Tip:

1. If the spray tip opening is clogged, do not use a pin or pointed object to unclog the tip. Unscrew the spray pump unit from the bottle by turning it counter-clockwise (to the left). See Figure 5.
2. Soak only the spray pump unit in warm water. Squirt several times while holding it under water. Use the pumping action to clear the opening in the tip. See Figure 6.

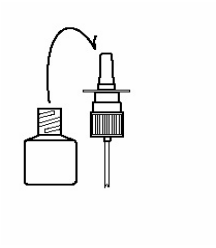

Figure 5

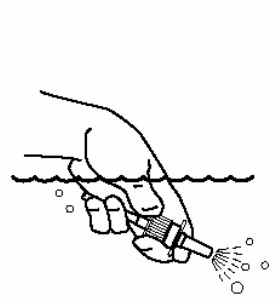

Figure 6

3. Let the spray pump unit air dry. Make sure it is dry before you put it back onto the bottle.
4. Put the spray pump unit back into the open bottle and tighten it by turning clockwise (to the right).
5. To keep the medicine from leaking out, use firm pressure when you put the pump back onto the bottle.
6. After cleaning, follow the instructions for priming.

Manufactured by
MEDA Pharmaceuticals
MEDA Pharmaceuticals Inc.
Somerset, NJ 08873

U.S. Patent Pending
<version code> Revised: mm/yy

Drafted: CCJ/ August 25, 2009
Initialed:
Barnes/ August 26, 2009
Limb/ August 26, 2009
Seymour/ August 26, 2009

Finalized: CCJ/ August 26, 2009

Filename: 22371 August 26 2009 Labeling Fax.doc

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/s/

COLETTE C JACKSON
08/26/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 14, 2009

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-564-2377	**Fax number:** 301-796-9718
Phone number: 973-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371 FDA Proposed Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-371
azelastine hydrochloride 0.15% nasal spray

Please refer to your August 1, 2008, new drug application (NDA) for azelastine hydrochloride 0.15% nasal spray. We acknowledge your submissions dated July 23, and August 11, 2009. We have the following preliminary labeling comments. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the revisions shown in the attached labeling and described below by COB August 17, 2009.

1. The heading for Section 14 has been changed back to "Clinical Studies" as prescribed by the PLR format.

2. The indications statement (1.1) has been modified to maintain consistency with the indications statement in the Highlights section as well as with labels for other products approved for use in allergic rhinitis.

3. Section 6.1 has been further updated to include the results of the completed long-term safety studies, MP432 for Astepro 0.1% and MP436 for Astepro 0.15%. Verify the demographic information for the updated Astepro 0.1% and 0.15% safety databases.

4. Section 6.1, Line 109: The total number of patients treated in the placebo controlled clinical trials has been corrected to maintain consistency with the numbers featured in Table 2.

5. We are currently reviewing the proposed changes to Table 3 submitted in the August 11, 2009, labeling communication. Additional comments will be forthcoming.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosure: FDA Proposed Labeling

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/s/

COLETTE C JACKSON
08/14/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: August 8, 2009

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-564-2377	**Fax number:** 301-796-9718
Phone number: 973-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371

Total no. of pages including cover: 3

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-371
azelastine hydrochloride 0.15% nasal spray

Please refer to your August 1, 2008, new drug application (NDA) for azelastine hydrochloride 0.15% nasal spray. We acknowledge your submission dated July 15, 2009. We have the following preliminary labeling comments. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the revisions shown in the attached labeling and described below by COB August 11, 2009.

1. Revise the immediate container labels for the Astepro 0.1% and 0.15% strengths to distinguish them from one another. It is likely that the patients don't keep the carton once dispensed.

2. The established name font should be at least half the size of the trade name.

3. Revise the trade name font and prominence to make it uniform with the strength. In order to avoid distraction, delete the broad arrow around the strength.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Project Manager, at 301-796-1230.

Drafted: CCJ/ August 7, 2009
Initialed:
Barnes/ August 7, 2009
Peri/ August 7, 2009
Al Hakim/ August 7, 2009

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/s/

COLETTE C JACKSON
08/08/2009

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

FACSIMILE TRANSMITTAL SHEET

DATE: July 17, 2009

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-564-2377	**Fax number:** 301-796-9718
Phone number: 973-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-371
azelastine hydrochloride 0.15% nasal spray

Please refer to your August 1, 2008, new drug application (NDA) for azelastine hydrochloride 0.15% nasal spray. We acknowledge your submission dated April 29, 2009. We have the following preliminary labeling comments. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the revisions shown in the attached labeling and described below by COB July 24, 2009.

1. We updated Section 6 to include the complete, 1-year safety data from the two long-term safety studies, MP432 and MP436.

2. Based on our evaluation of the multiple dose PK study (Study 25), azelastine hydrochloride did not demonstrate dose proportionality or time-independent PK due to the large variability of the data leading to inconsistent results in these analyses. Delete the statement about the dose proportionality in Section 12.3 of the label.

3. We simplified Sections 8, 10, and 13 by deletion of the product strengths and inclusion of only the most conservative dose ratios.

4. We have added instantaneous TNSS scores to support the new once daily dosing regimen.

5. The data values presented in Table 6 are based on our reanalysis of the data using ANCOVA. Only the ITT analysis is shown; we removed the per protocol population analysis.

6. We reorganized Section 17 by order of clinical importance.

7. If you intend to print the Patient Information section at the end of labeling, the section should be included in Section 17 under the subsection heading "17.6 FDA-Approved Patient Labeling." If you plan to print this information separately or it is to be detached, it does not need to be included under Section 17.

8. The information presented in the patient package insert should be consistent with information presented in the product label, and no additional information should be included in the PPI. For example, we note that only the PPI includes recommendations in case of accidental ingestion by a child; add a corresponding recommendation to the PI or delete. Other changes have been made to ensure consistency.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Project Manager, at 301-796-1230.

Enclosure: FDA Proposed Labeling

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/s/

Colette Jackson
7/17/2009 05:40:13 PM
CSO

INTEROFFICE MEMO

TO: NDA 22-371 (0.15% Azelastine HCl Nasal Spray)
Amendment dated April 29, 2009

FROM: Timothy W. Robison, Ph.D., D.A.B.T.
Senior Pharmacology/Toxicology Reviewer
Division of Pulmonary and Allergy Products

DATE: July 8, 2009

The Amendment dated April 29, 2009 contained no nonclinical data. Further, nonclinical sections of the labeling were unchanged. A nonclinical review of the Amendment dated April 29, 2009 is not needed. Please refer to Dr. Luqi Pei's Review dated April 20, 2009.

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/s/

Timothy Robison
7/8/2009 11:21:18 AM
PHARMACOLOGIST

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: x YES NO

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
J. Richard Trout, Ph.D., Consultant Statistician

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-treament 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.*

Discussion:

MedPointe asked the Division to clarify its PK requirements. The Division stated that the purpose of the study is to support the safety of the drug since the proposed pivotal trial is only 2 weeks. MedPointe needs to show whether the new formulation has an effect on the bioavailability of the drug. The Agency stated that although bioequivalence between the new formulation and the old formulation is not being pursued, 90% confidence intervals of the ratio of relevant PK parameters between the formulations should be reported, At least 12 patients per subgroup would be needed, and it is recommended that blood samples to describe the full PK profile be taken on all groups due to the fact that the drug has a long half life. It is acceptable to use healthy subjects.

Pediatric Program

Question A. *In order to comply with PREA, MedPointe proposes to use the study design options described in your September 20, 2002 Astelin® Pediatric Written Request as the basis of our sweetened formulation pediatric study. Does the Division agree with this approach?*

Question B. *Assuming a pediatric study (as outlined in September 20, 2002 Pediatric Written Request) is conducted and leads to an approved SAR indication in children 2 years of age and older, would there be an additional 6-months of pediatric exclusivity?*

Response: *Our responses to your questions regarding your Pediatric Program are not included here. If available before the meeting, we will forward our responses to you.*

Discussion:

The Division stated that we will defer this discussion until a later time. The Division did note that for any drug product, it is necessary to conduct studies down to the age where the disease exists.

Toxicology Requirements

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

Response: *No, the Division does not agree. Additional toxicology evaluations are required in order to qualify the safety of inhaled sucralose and the significant change in the product formulation. To adequately evaluate the product, the following studies are needed:*

1. *One (1) 6-month intranasal toxicity study of sucralose and one (1) 3-month bridging intranasal toxicity study of the sweetened formulation in the most appropriate species, or*

2. *One (1) 6-month intranasal toxicity study of the sweetened formulation in the most appropriate species.*

Additional toxicity studies may be needed pending the results of the recommended studies. For example, the observation of proliferative or preneoplastic changes in chronic toxicity studies with sucralose may warrant the conduct of a carcinogenicity study via the intranasal route.

The studies should be designed to adequately evaluate the toxicity profile of sucralose and the sweetened formulation in the respiratory tract. An adequate evaluation should include establishment of a no-observed-adverse-effect-level (NOAEL) for sucralose via the intranasal route, sufficient safety margins for sucralose in humans based on the animal data, and an evaluation of potential toxicological interactions between sucralose and the active ingredient.

Species selection for these 6- and 3-month studies should be based on the results of shorter term studies (generally 2-4 weeks in duration) in 2 species which include at least one non-rodent species. Consultation with the Division regarding the study designs prior to study initiation is encouraged.

Intranasal toxicity studies of the sweetened formulation with a treatment duration at least equal to that of intended clinical trials should be completed prior to the initiation of such trials. Therefore, studies of at least 2 weeks duration using the proposed formulation in 2 species should be submitted to support the proposed 2-week clinical trial. The recommended 3- and 6-month studies should be submitted to support any longer duration clinical trials and an NDA submission.

The safety qualification of impurities, degradants, leachables and extractables, if applicable, should be addressed in the NDA submission.

The above recommendations are based on our determination that the rationales provided in the briefing package for not conducting additional toxicity studies are insufficient to support the safety of chronic intranasal use of the sweetened formulation. The rationales include: 1) The toxicity of Astelin® is well characterized in NDA 20-114; 2) Sucralose is safe to use as a food additive. The material safety data sheet (MSDS) of sucralose does not identify any special risk for inhalation exposure. A 2-week intranasal irritation study with (b) (4) *sucralose in rats did not reveal any significant adverse reactions; and 3) Clinical studies will evaluate the safety of the formulation. These rationales are insufficient to support the safety of chronic clinical use of the sweetened formulation due to the lack of animal toxicity studies to adequately evaluate the intranasal use of the formulation and its components for the reasons described below.*

Data obtained from the development of Astelin Nasal Spray is not sufficient to support the safety of the sweetened formulation because the

two formulations have significantly different compositions. The sweetened formulation contains three ingredients (i.e., (b) (4) sucralose, (b) (4) sorbitol and (b) (4)) that are not present in the Astelin® nasal spray. Significant formulation differences may alter the safety profile of the final drug product. The safety profile of the sweetened formulation is unknown because no toxicity studies have been completed with the sweetened formulation. Consequently, the nonclinical program for Astelin® Nasal Spray is considered insufficient to support the safety of the sweetened formulation.

The safety of the chronic intranasal use of sucralose, a component of the sweetened formulation, has not been established. Sucralose has not been approved for any intranasal products although it is considered safe to be used as a food additive and for oral consumption. The difference in routes of administration might affect the toxicity of sucralose, especially regarding the local toxicity. The lack of special cautionary measures to prevent inhalation exposure of sucralose as indicated in the MSDS is not adequate to alleviate concerns about the safety of chronic intranasal use of the compound. Also, the completed 2-week intranasal study in rats (Study No. 16365) suggests that sucralose may enhance the irritation induced by azelastine HCl as the addition of (b) (4) sucralose to Astelin® nasal spray increased the incidence of acute multi-focal inflammation in males and goblet cells hypertrophy/hyperplasia in females. These findings are a potential safety concern and additional toxicity studies are needed to alleviate this concern. Therefore, the safety of chronic intranasal use of sucralose needs to be supported by adequate nonclinical data using the appropriate route of administration.

The sorbitol concentration in the sweetened formulation is significantly higher than that in approved intranasal drug products. Clinical evaluation alone is not considered adequate to evaluate the safety profile of a drug product. The nonclinical safety of the sweetened formulation must be demonstrated and the recommended animal toxicity studies should be designed to achieve this goal.

Discussion:

MedPointe stated that they understand the issues related to sucralose, and they do have their shorter term studies completed (1 rodent, 1 non-rodent) and they did not see any concerning findings. MedPointe asked the Division if the previously submitted rat study would satisfy one of the two studies required. The Division stated that the study as it was would not satisfy as one of the 2 studies required for 2 reasons:

1. The study did not appear to test the intended clinical formulation. The study report was not specific about the composition of the vehicle. It appeared that the vehicle was the old formulation (Astelin®) spiked with sucralose. Studies with

the intended clinical formulation are needed to support the clinical use of such formulations.

2. The study did not establish a NOAEL for the formulation. The rats treated with either 0.1% or 0.15% azelastine HC in presence of (b) (4) sucralose showed increased incidences of nasal lesions than those treated with the vehicle, vehicle plus sucralose, or Astelin®. The finding suggests a potential synergistic toxicological interaction between sucralose and azelastine. Such an interaction is of safety concern. Consequently, a NOAEL for the formulation is needed for its safety evaluation.

MedPointe stated that the new formulation was used. MedPointe agreed to submit the composition of the formulation used in the study to the IND for review. The Division could follow up with a teleconference for further discussion, if necessary.

MedPointe disagreed with the Division's conclusion that the NOAEL for the formulation has not been established. MedPointe reasoned that the increased incidence of nasal lesions was seen in the groups of interest because the Astelin control groups, especially the females, showed unexpectedly low incidences of the lesion. Furthermore, the incidence and type of lesions observed in the groups with both azelastine and sucralose were well within the historic background values. MedPointe agreed to submit the histological data for the Division to review.

MedPointe sought clarifications on the establishment of a NOAEL for sucralose in rats. MedPointe stated that a NOAEL has been established because no nasal lesions were observed in the group treated with the vehicle in presence of sucralose. The Division agreed with the sponsor that (b) (4) ucralose did not affect the toxicity of vehicle but disagreed with the conclusion that the NOAEL for sucralose was established because of toxicity associated with the formulation containing the same concentration of sucralose. The Division pointed out that the groups treated with sucralose and azelastine showed increased incidence of nasal lesions than the vehicle plus sucralose. The Division interpreted the above finding as a sign of potential synergistic toxicological interactions between sucralose and azelastine. Since the findings associated with the formulation are more relevant to the safety evaluation, the lack of NOAEL in the formulation would be translated into a lack of NOAEL for sucralose. Further, it is premature to conclude that a NOAEL for chronic use of sucralose has been established because the 2 week toxicity studies are not always predictive of the response to chronic exposure. Thus, MedPointe should design studies to attempt to establish a NOAEL for sucralose. Ideally, different doses of sucralose should be employed.

MedPointe agreed to submit all available evidence for the Division to review. The Division would determine that acceptability of the 2-week rat study upon reviewing additional data. If the additional data are deemed satisfactory, the completed 2-week in rats can be considered satisfactory to meet the requirement for the 2-week study in a rodent species. If the additional data are not considered adequate, MedPointe will have to perform an additional 2-week rodent study.

The Division encouraged MedPointe to submit the study protocols for comments. MedPointe stated they will put together a protocol and submit for a later discussion.

Once MedPointe clarifies and documents the formulations of the study, a later discussion can be held concerning the dog studies. The Division stated that once the formulation and histological data is submitted, a NOAEL can be evaluated.

MedPointe asked if the animal studies need to be conducted prior to the start of their clinical trials. The Division stated that the supporting animal studies should be conducted prior to the start of the clinical studies for the new formulation. Draft reports may be initially submitted followed by the finalized reports.

MedPointe stated that they do intend on having a CMC meeting at a later date. They understand the requirements for full characterizations needed and they will comply.

MedPointe summarized the major points of discussion:

1. MedPointe will use a comparability clinical study design, using 5 arms. They will compare active versus placebo and they will eyeball the dose response curves.

2. MedPointe will include baseline values as covariate in their model.

3. The PK data is supportive for safety. There is large variability in the PK data, and MedPointe will use 90% confidence interval limits in its comparisons. MedPointe will look for directional changes. The use of healthy volunteers and at least 12 subjects is acceptable for the purpose of PK comparisons between formulations.

4. MedPointe will provide clarification of the formulations used in the toxicology studies. MedPointe will provide a new protocol for the dog and will follow up with a future teleconference for discussion. MedPointe acknowledges the Division's requirement for a second toxicology study.

5. MedPointe will defer the pediatric discussion until a later time.

Minutes Preparer
Colette Jackson

Drafted by: CCJ/May 20, 2005

Initialed by: Pei/May 23, 2005
McGovern/ May 27, 2005
Suarez/ May 26, 2005
Fadiran/ May 26, 2005
Gebert/ May 23, 2005
Purohit-Sheth/ May 27, 2005
Gilbert-McClain/ May 27, 2005
Chowdhury/ June 9, 2005

Finalized: CCJ/June 9, 2005

Filename: I69785 preP3 MM

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/s/

Colette Jackson
6/9/05 03:45:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-371

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

Attention: Richard Fosko, R.Ph., MPH
Director, Regulatory Affairs

Dear Mr. Fosko:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azelastine Hydrochloride 0.15% w/v Nasal Spray.

We also refer to your May 15, 2009, correspondence, received May 18, 2009, requesting a meeting to seek clarification as to the basis for the denial of your proposed proprietary names Astepro (b) (4).

The meeting is scheduled for:

Date: June 3, 2009
Time: 3:00 PM, EST
Phone Arrangements: FDA will call MEDA at 866-742-1857.

CDER Participants will be:

Carol Holquist, R.Ph.	Director, Div. of Medical Error Prevention and Analysis
Denise Toyer, Pharm D	Deputy Director, DMEPA
Kellie Taylor, Pharm D	Team Leader, DMEPA
Zachary Oleszczuk, Pharm D	Safety Evaluator, DMEPA
Sean Bradley, R.Ph.	Regulatory Safety Project Manager, OSE
Badrul Chowdhury, MD	Director, Div. of Pulmonary and Allergy Products
Sally Seymour, MD	Team Leader, DPAP
Susan Limb, MD	Medical Officer, DPAP
Colette Jackson	Regulatory Project Manager, DPAP

If you have any questions, call Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 796-1332.

Sincerely,

{See appended electronic signature page}

Sean Bradley, R.Ph.
Regulatory Safety Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Sean Bradley

6/1/2009 02:55:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 22-371

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

Attention: Richard Fosko
Director, Regulatory Affairs

Dear Mr. Fosko:

Please refer to your August 1, 2009, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for azelastine 0.15%.

On April 30, 2009, we received your April 29, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 1, 2009.

If you have questions, call Colette Jackson, Senior Regulatory Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sandra Barnes

5/19/2009 05:26:31 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2009

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-564-2377	**Fax number:** 301-796-9718
Phone number: 973-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371 FDA Proposed Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-371
azelastine hydrochloride nasal spray 0.15%.

Please refer to your August 1, 2008, new drug application (NDA) for azelastine hydrochloride nasal spray 0.15%. Please refer to the enclosed labeling with our preliminary labeling comments and/or recommendations outlined below. The labeling recommendations pertain primarily to the use of the tradename, organization of the label, and the clinical sections. The FDA-proposed revisions to your draft labeling have been made using the clean copy of the Word version of the label submitted on April 10, 2009. FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling.

1. Section 6 has been updated to include the completed, 1-year safety data from the two long-term safety studies, MP432 and MP436.

2. Sections 8, 10, and 13 have been simplified by deletion of the product strengths and inclusion of only the most conservative dose ratios.

3. The data values presented in Table 4 are based on the Agency's reanalysis of the data using ANCOVA. Only the ITT analysis is shown; the per protocol population analysis has been removed.

4. If you intend to print the Patient Information section at the end of labeling, the section should be included in Section 17 under the subsection heading "17.6 FDA-Approved Patient Labeling." If you plan to print this information separately, it does not need to be included under Section 17.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosure: Recommendations to the Proposed Labeling

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/s/

Colette Jackson
5/1/2009 04:22:53 PM
CSO

Public Health Service
DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

Memorandum

DATE: April 17, 2009

TO: Division File System

FROM: Prasad Peri, Ph.D,

SUBJECT: NDA 22371 Final recommendation from the Office of Compliance regarding Establishments listed in the NDA.

Note that the primary (Dr. Martin Haber dated 3-11-2009) and secondary review (Dr. Ali Al Hakim, dated 3-11-2009) were placed into DFS prior to the final recommendation provided by the Office of Compliance. The final recommendation from the office of compliance was provide to the Division on 3-18-2009 and the recommendation is acceptable.

Based on this final recommendation, the recommendation from CMC for this NDA is approval.

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/s/

Prasad Peri
4/17/2009 09:27:10 AM
CHEMIST

Ali Al-Hakim
4/17/2009 09:29:53 AM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 31, 2009

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-564-2377	**Fax number:** 301-796-9718
Phone number: 973-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371 Comments and Requests for Information

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-371
azelastine hydrochloride 0.15% nasal spray
MEDA Pharmaceuticals

We are reviewing your August 1, 2008, new drug application (NDA) for azelastine hydrochloride 0.15% nasal spray. We have the following comments and requests for information. Please respond by COB April 3, 2009, in order to facilitate our review of your NDA.

1. The Integrated Summary of Safety reports that 2 SAR patients receiving MP03-36 discontinued prematurely due to an abnormal test results. Identify the individual studies and patients and provide the corresponding lab data and any follow-up, if available.

2. In Study MP436, Patients 021-004 and 063-004 each had marked CK elevations at the 6-month visit. Provide any clinical or laboratory follow-up available for these patients.

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Drafted: CCJ/ March 27, 2009
Initialed:
Barnes/ March 30, 2009
Limb/ March 30, 2009
Seymour/ March 30, 2009

Finalized: CCJ/ March 31, 2009

Filename: 22371 March 2009 MO Fax.doc

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/s/

Colette Jackson
3/31/2009 01:52:42 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: March 20, 2009

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA Pharmaceuticals	Division of Pulmonary and Allergy Products
Fax number: 973-564-2377	**Fax number:** 301-796-9718
Phone number: 973-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371 FDA Proposed Labeling

Total no. of pages including cover:

Comments:

Document to be mailed: **YES** **xNO**

NDA 22-371
azelastine hydrochloride 0.15% nasal spray.

Please refer to your August 1, 2008, new drug application (NDA) for azelastine hydrochloride 0.15% nasal spray. Please refer to the enclosed labeling with our preliminary labeling comments and/or recommendations outlined below. The labeling recommendations pertain primarily to the use of the tradename, organization of the label, and the clinical sections. The FDA-proposed revisions to your draft labeling have been made using the clean copy of the Word version of the label submitted on February 20, 2009. FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all inclusive and we may have additional comments. Submit revised draft labeling incorporating the changes outlined in our enclosed labeling.

1. Change Astepro and Astepro (b) (4) to Astepro 0.1% and Astepro 0.15%. The tradename remains under review so these changes are tentative at this time. These changes have been done in the Highlights, Indications and Usage, and Dosage and Administration sections. Revise the remainder of the sections of the label accordingly.

2. Reorganize each section of the label so that information for the lower concentration, Astepro 0.1%, is provided before Astepro 0.15% unless otherwise indicated.

3. Indications and Usage and Dosage and Administration information should be organized by indication (SAR and PAR), not by drug concentration level. See highlighted changes.

4. Remove data on the once daily regimen from the Adverse Reactions Section 6 and the Clinical Trials Section 14.

5. Combine the adverse reactions listed in the Highlights section since the events for each dose are similar and there does not appear to be a clear dose-related frequency. The Adverse Events section should remain organized by dose level, excluding the once-daily dosing regimen for Astepro 0.15%.

6. For the Clinical Trials section, organize by indication not by formulation: SAR followed by PAR (see changes). Fill in blanks and tables where indicated.
    - SAR
        - Astepro 0.1% results as in current product label
        - Astepro 0.15%: results for Study MP433 (minus the once daily arm) and MP438
    - PAR
        - Astepro 0.15%: results for Study MP434

7. Combine the Patient Information section for the 2 dosage strengths into one Patient Information section.

8. When finalized, you will need to revise the tradename on carton and bottle labels for both NDAs.

9. Your calculation of the amount of azelastine free base per spray appears incorrect. Revise to 187 mcg per spray actuation, not (b) (4)

If there are any questions, please contact Ms. Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Enclosure: Recommendations to the Proposed Labeling

20 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

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/s/

Colette Jackson
3/20/2009 05:54:52 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-371

INFORMATION REQUEST LETTER

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

Attention: Richard Fosko
Director, Regulatory Affairs

Dear Mr. Fosko:

Please refer to your new drug application (NDA) dated August 1, 2008, received August 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (azelastine hydrochloride 0.15%) Nasal Spray.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The following comments refer to the primary efficacy analysis in Study MP434 for the PAR indication, specifically, Table 7 under Section 11.4.1.1 of the study report.

   a. Provide the SAS program used to compute the p-values and 95% confidence intervals for the comparisons between the active treatments and placebo. The program should not call any SAS macros; in other words, it should run by itself.

   b. Clarify the data sets and variables used in the analysis. We assume that you used the data set named D_TNSS which includes the primary efficacy variable and D_EVAL which includes variable RXGRP representing the treatments.

   c. Provide the same analysis for the comparison between MP03-33 and placebo for p-value and 95% confidence intervals as you did for the comparison between MP03-36 and placebo.

2. The chemistry, manufacturing and controls information you provided for NDA 22-371 (azelastine HCl, 0.15%, Nasal Spray) is almost identical to the information you provided for your approved NDA 22-203 (azelastine HCl, 0.1%, Nasal Spray) with the exception of the description of the final solution strength (0.15% instead of 0.1%). Provide a discussion listing, identifying and justifying all CMC changes (i.e., new information) in NDA 22-371 that differs from CMC information you provided previously for NDA 22-203. Certify that these identified changes are the only CMC changes made and that all other CMC information remains the same as previously submitted.

Please respond to our comments by COB January 12, 2009. If you have any questions, call Colette Jackson, Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sandra Barnes

1/6/2009 06:05:28 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-371

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

Attention: Richard Fosko
Director, Regulatory Affairs

Dear Mr. Fosko:

Please refer to your new drug application (NDA) dated August 1, 2008, received August 1, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (azelastine hydrochloride 0.15%) Nasal Spray.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 1, 2009.

During our filing review of your application, we identified the following potential review issues:

1. The adequacy of the application to support the approval of MP03-36 for SAR will be a review issue. Upon preliminary review, the application does not demonstrate a statistically significant efficacy advantage for MP03-36 over MP03-33 to justify the approval of both dosage strengths. As noted in the September 28, 2006, meeting minutes for IND 69,785, *"If both formulation are efficacious, there will be no reason to approve the higher strength without demonstration of efficacy or safety advantage over the lower strength."* Furthermore, your submission of separate labels for the same product with different dosage strengths (MP03-36 under NDA 22-371 and MP03-33 under NDA 22-203) is problematic as both MP03-36 and MP03-33 share the same proposed SAR indication without clear dosing guidelines. The use of separate tradenames also raises a safety concern because health care providers may fail to recognize that the products contain the same active ingredient and patients may be unintentionally overdosed.

2. The adequacy of the application to support a PAR indication will be a review issue. Upon preliminary review, neither Study MP434 or MP435 appear to have demonstrated a statistically significant difference from placebo in terms of the pre-specified primary endpoint.

3. The adequacy of the application to support a once-daily dosing regimen for SAR will be a review issue. According to the Draft Guidance for Industry, Allergic Rhinitis: Clinical Development Programs for Drug Products, the sponsor should demonstrate a significant difference in the instantaneous symptoms scores between the drug and placebo at the end of the dosing interval. Upon preliminary review, of the 3 SAR trials conducted to support the once daily dosing, only Study MP440 had AM iTNSS scores that support the once daily dosing interval. Study MP439 and Study MP433 failed to show a statistically significant difference for the AM iTNSS between MP03-36 and placebo. In addition, Study MP433 was not appropriately designed to assess the once daily dose, as the once-daily MP03-36 arm also received a PM placebo nasal spray which could confound efficacy findings.

We are providing the above comments to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also have the following requests for information.

4. The submission lacks multiple-dose PK information for 0.15% sweetened azelastine hydrochloride. Assuming that you do not have such data for the new formulation, please provide the following:

    a. Clarification on whether azelastine exhibits time-independent pharmacokinetics in the proposed dose range. You need to address whether the steady-state PK can be predicted from the single dose PK data for 0.15% sweetened azelastine hydrochloride.

    b. Multiple dose PK data in healthy and/or the indicated patient population for the currently marketed 0.1% Astelin® product.

5. Provide results from in vitro dose proportionality (e.g., spray content uniformity, spray weight, spray volume etc.) studies between the two strengths (0.10% and 0.15% azelastine hydrochloride nasal spray) of the drug product.

6. Provide samples of the drug product in your proposed commercial packaging configuration.

7. Provide draft mockups (100 % size) of the proposed carton, container labels.

8. Provide a statement to the NDA to indicate that all sites are ready for inspection.

9. The following comments pertain to the Highlights section of the product label. Please address the identified deficiencies/issues and re-submit the labeling. This updated version of labeling will be used for further labeling discussions.

   a. Use the "TM" symbol only once in the content of labeling.

   b. For pregnancy category C drugs, pregnancy must be listed under the Use in Specific Populations in the Highlights followed by the following statement: "Based on animal data, may cause fetal harm"

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients less than 12 years of age.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Badrul Chowdhury

10/14/2008 01:35:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Colette Jackson
Project Manager
Division of Pulmonary and Allergy Products, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 15, 2008		22-371	N	September 5, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(b) (4)	Standard	Antihistamine Nasal Spray	April 1, 2009

NAME OF FIRM: MEDA Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a request for a tradename consult for NDA 22-371. MEDA submitted only one name for review- (b) (4). The newly proposed name is included in MEDA's September 5, 2008, paper submission attached with this consult. The PI is electronic under the submission dated August 1, 2008. The PI has not been updated to reflect the proposed name.

PDUFA DATE: June 1, 2009
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-371
HFD-570/Division File
HFD-570/RPM
HFD-570/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)

Colette Jackson 6-1230	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

Colette Jackson
9/15/2008 06:07:04 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Division of Drug, Marketing, Advertising and Communication (DDMAC)
WO Bldg 22 Rm. 1400

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Sadaf Nabavian (for Colette Jackson)
Project Manager
Division of Pulmonary and Allergy Products at 6-1230

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 03, 2008		22-371	N-000 (new NDA)	August 01, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Azelastine Hydrochloride 0.15% Nasal Spray	Standard	Antihistamine (H1 receptor antagonist)	February 01, 2008

NAME OF FIRM: Meda Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

This is a request for an evaluation and review of the package insert and patient product information for azelastine hydrochloride 0.15% nasal spray. The submission is located in the EDR dated August 01, 2008.
This submission is seeking a higher concentration of azelastine hydrochloride (0.15%) than the current marketed azelastine hydrochloride nasal spray (0.1%). The new formulation also contains a taste masking agent sucralose.
PDUFA DATE: June 01, 2009

SIGNATURE OF REQUESTOR
Sadaf Nabavian (for Colette Jackson)

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Sadaf Nabavian

9/3/2008 04:20:39 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Sadaf Nabavian (for Colette Jackson)
Division of Pulmonary and Allergy Products (HFD-570)
301-796-1230

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 03, 2008		22-371	N-OOO (original)	August 1, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Azelastine hydrochloride 0.15% Nasal Spray	Standard	Antihistamine (H1 receptor antagonist)	February 1, 2008

NAME OF FIRM: Meda Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a consult for a labeling review of the package insert and patient product information for azelastine hydrochloride 0.15% NS. The new NDA is seeking a higher concentration of azelastine hydrochloride (0.15%) than the current marketedazelastine hydrochloride nasal spray (0.1%). The new formulation also contains a taste masking agent sucralose. The package insert and the patient product information are also electronic and located in the EDR under the submission dated August 01, 2008.

PDUFA DATE: June 01, 2009

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sadaf Nabavian (for Colette Jackson)	☐ MAIL X Email ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Sadaf Nabavian

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-371

NDA ACKNOWLEDGMENT

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

Attention: Richard Fosko, R.Ph., MPH
Director, Regulatory Affairs

Dear Mr. Fosko:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product:	Azelastine hydrochloride 0.15% nasal spray
Date of Application:	August 01, 2008
Date of Receipt:	August 01, 2008
Review Priority Classification:	Standard
Our Reference Number:	NDA 22-371

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 30, 2008, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

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

Sincerely,

{See appended electronic signature page}

Colette Jackson
Regulatory Health Project Manager
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sadaf Nabavian

8/21/2008 02:50:19 PM

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 3, 2008

To: Richard Fosko	**From:** Colette Jackson
Company: MEDA	Division of Pulmonary and Allergy Products
Fax number: 732-564-2377	**Fax number:** 301-796-9718
Phone number: 732-564-2358	**Phone number:** 301-796-1230

Subject: NDA 22-371 January 5, 2009, Teleconference Meeting Minutes

Total no. of pages including cover: 4

Comments:

Document to be mailed: **YES** x**NO**

MEMORANDUM OF TELECON

DATE: January 5, 2009

APPLICATION NUMBER: NDA 22-371

BETWEEN:

Name: MEDA Pharmaceuticals Representatives:

Harry Sacks, M.D., Vice President, Medical and Scientific Affairs
Richard Fosko, Director, Regulatory Affairs
Cary Sax, Associate Director, Regulatory Affairs
Bill Wheeler, Ph.D., Director, Clinical
Carrie D'Andrea, Associate Director, Clinical
Cindy Yayac, Manager, Regulatory Affairs

Phone: 1-866-742-1857
Representing: MEDA Pharmaceuticals

AND

Name: FDA Representatives:

Division of Pulmonary and Allergy Products:

Sally Seymour, M.D., Deputy Director for Safety/Clinical Team Leader
Colette Jackson, Regulatory Health Project Manager

Division of Medication Error Prevention and Analysis:

Carol Holquist, RPh, Division Director
Denise Toyer, PharmD, Deputy Division Director
Todd Bridges, RPh Safety Evaluator
Zachary Oleszczuk, PharmD, Safety Evaluator
Tselaine Jones-Smith, PharmD, Safety Evaluator
Sean Bradley, Project Manager
Darrell Jenkins, Team Leader, Project Management

SUBJECT: Tradename for NDA 22-371

BACKGROUND:

MEDA submitted a new drug application (NDA) on August 1, 2008, for (b) (4), which is a higher strength (0.15%), sweetened formulation of azelastine hydrochloride nasal spray. MEDA

is seeking approval of this application in patients 5 years of age and older for the treatment of symptoms of seasonal allergic rhinitis and perennial allergic rhinitis in patients 12 years of age and older. Astepro, a sweetened azelastine (0.1%) formulation was approved on October 15, 2008. This teleconference discussed the proposed tradename, (b) (4).

DISCUSSION:

The FDA opened the discussion and referred to the 74-day letter sent to MEDA on October 14, 2008. In comment #1 of the letter, it states "*The use of separate tradenames also raises a safety concern because health care providers may fail to recognize that the products contain the same active ingredient and patients may be unintentionally overdosed.*" The FDA asked MEDA if they intend to address this comment. MEDA stated that they have conferred with their commercial team and are awaiting additional names to provide to the FDA. The FDA expressed concern over the use of 2 different proprietary names for the sweetened azelastine hydrochloride product given the October 15, 2008, approval of Astepro, a sweetened, 0.1% formulation of azelastine hydrochloride. MEDA needs to consider the use of one proprietary name since Astepro and (b) (4) are different strengths of the same product. The differences in strengths can be highlighted in the labeling to distinguish the two products. MEDA stated they would discuss this with their commercial team and get back to the FDA.

The FDA asked MEDA for an anticipated timeframe for response and reminded MEDA that their response needs to be submitted as soon as possible to allow sufficient time for review. Also, if all of the product information will be in one label, MEDA would need to revise the PI significantly to incorporate Astepro and to figure out how to differentiate the strengths. If MEDA decides to maintain the use of 2 different names for their sweetened azelastine products, they would need to provide a rationale as to how to handle the dual tradename in the marketplace. If MEDA decides to use any modifiers, those modifiers need data to support its use and to show that the proposed modifiers or suffixes will have a well recognized meaning, conveys accurate information about the product differences, and will not be similar in sound or appearance to another established or proprietary name. MEDA stated they will discuss this internally and get back to the FDA.

_____

Colette Jackson
Regulatory Health Project Manager

Drafted: CCJ/ January 26, 2009
Initialed:
Seymour/ January 26, 2009
Toyer/ January 26, 2009
Holquist/ January 26, 2009

Finalized: CCJ/ February 3, 2009

Filename: 22371 January 5 2009 tradename tcon MM.doc

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/s/

Colette Jackson
2/3/2009 06:40:13 PM
CSO

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

FACSIMILE TRANSMITTAL SHEET

DATE: September 28, 2006

To: Richard Fosko	**From:** Colette Jackson
Company: MedPointe Pharmaceuticals	Division of Pulmonary and Allergy Drug Products
Fax number: 732-564-2361	**Fax number:** 301-796-9718
Phone number: 732-564-2358	**Phone number:** 301-796-1230

Subject: IND 69,785 August 29, 2006, Meeting Minutes

Total no. of pages including cover:

Comments: Protocol comments

Document to be mailed: x YES NO

IND 69,785
Drug: Azelastine Hydrochloride Nasal Spray
Sponsor: MedPointe Pharmaceuticals
Date of Meeting: August 29, 2006

MedPointe Representatives:

Richard N. Spivey, Pharm D, Ph.D., Senior Vice President, Research & Development
Harry J. Sacks, M.D., Senior Director, Medical Affairs
Michael Bernhard, Ph.D., Senior Director, Regulatory Affairs
Richard Fosko, R.Ph., MPH, Associate Director, Regulatory Affairs
Anthony Coniglio, Pharm D, Vice President, Business Development and Portfolio Optimization

Division of Pulmonary & Allergy Products Representatives:

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Susan Limb, M.D., Clinical Reviewer
Lydia Gilbert-McClain, M.D., Medical Team Leader
Sally Seymour, M.D., Acting Medical Team Leader
Sayed Al Habet, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer
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
Ruthanna Davi, M.S., Statistical Team Leader
Colette Jackson, Project Manager

Background: MedPointe submitted a meeting request dated May 25, 2006, to discuss their proposed preclinical and clinical programs for a higher strength sweetened azelastine hydrochloride nasal spray formulation. MedPointe submitted a briefing package containing questions to be discussed at this meeting on July 28, 2006. The Division responded to those questions by sending a telephone facsimile dated August 17, 2006. The content of this telephone facsimile is printed in *italics* below. Any discussions are captured directly under each response in normal font.

Clinical Questions:

3.0 Question: Clinical Trials and Indications

The currently marketed Astelin (B Nasal Spray (NA 20-114) is indicated for the treatment of the symptoms of seasonal allergic rhinitis (SAR) in adults and children 5 years and older, and for the treatment of the symptoms of vasomotor rhinitis (VMR) in adults and children 12 years and older. For the higher strength azelastine nasal spray we will seek an indication for perennial allergic rhinitis (PAR) in addition to the current indications (SAR (b) (4)). In order to evaluate the efficacy and safety of MP03-36 for these (b) (4) indications, MedPointe proposes to conduct the following two studies:

Our first clinical trial will be a 4-arm study in SAR patients, as follows:

- *MP03-36: 2 sprays in each nostril once daily (AM) plus 2 sprays placebo once daily (PM)*
- *MP03-36: 2 sprays in each nostril twice daily*
- *Current Astelin Nasal Spray: 2 sprays in each nostril twice daily*
- *Placebo: 2 sprays in each nostril twice daily*

For our second study, we propose a 3-arm PAR study, as follows:

- *MP03-36: 2 sprays in each nostril once daily (AM) plus 2 sprays placebo once daily (PM)*
- *MP03-36: 2 sprays in each nostril twice daily*
- *Placebo: 2 sprays in each nostril twice daily*

(b) (4)

Does the Division agree?

FDA Response:

(b) (4)

Discussion:

(b) (4)

4.0 Question: Long-Term Safety Study

We will also conduct a long-term safety study of MP03-36 providing data from a minimum of 300 patients treated for 6 months and 100 patients treated for 1 year, in

accordance with the International Conference on Harmonisation guidance El "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life- Threatening Conditions" (March 1995). We plan to submit the sNDA with 6-month safety data and to amend the supplement with 12-month data in accord with this ICH guidance. The study will be conducted as an open label extension of the PAR study described previously in Question 3. Spontaneously reported adverse events will be evaluated and direct visual nasal examination will be performed at each visit to assess the possibility of nasal irritation. We believe this approach is adequate to assess the long-term safety of the higher strength azelastine formulation.

Does the Division agree?

FDA Response:

No. The Division expects that all safety data supporting the supplemental application will be complete at the time of submission.

Discussion:

MedPointe asked why they needed 12 months of safety data at the time of the submission. The Division referred to the GRMP guidance document which states that the NDA must be complete at the time of submission. Submitting 6 months of safety data with the sNDA, with an additional 6-months of data submitted at the 4-month safety update is not acceptable. MedPointe requested feedback from the Division as to the length of patient exposure that is adequate for submission. The Division stated that MedPointe needs to submit as much data as they feel necessary to support the application in the original NDA submission.

Additional Clinical comments:

1. *Clarify the rationale for parallel clinical development of two different strength formulations of azelastine (MP03-33 and MP03-36) in two separate development programs with similar indications and dosing regimens. If both formulations are efficacious, there will be no reason to approve the higher strength without demonstration of efficacy or safety advantage over the lower strength.*

Discussion:

MedPointe stated that their intentions are to improve the profile of the drug. The currently marketed product has a bitter taste and in attempts to improve the taste, MedPointe presented a special protocol assessment (study MP430) in September 2005, for a sweetened formulation (MP03-33), which contains 0.1% azelastine, (b) (4) sucralose and sorbitol. If this study is successful, MedPointe will submit an sNDA, proposing 1-2 sprays of MP03-33 BID. The MP03-36 program utilizes a product with a higher strength sweetened formulation containing 0.15% azelastine,

(b) (4) sucralose, and sorbitol. The purpose of the higher strength formulation is to determine if there is improved efficacy over the currently marketed product or efficacy if administered once daily.

2. *The proposed designs of the 4-arm SAR and 3-arm PAR studies will be inadequate for establishing efficacy of once-daily dosing of MP03-36 because the placebo used for the afternoon dose may confound the efficacy findings.*

Discussion:

MedPointe stated that they understand the Division's concern. The proposed trial was designed to blind the patients. The Division stated that the placebo used could be effective. Also, the way the study is designed is not how the drug will be used when it is marketed. The Division suggested that MedPointe do an exploratory study with QD dosing.

In addition, the Division noted that there is concern with using the currently marketed azelastine product as the active comparator. The Division indicated that it is unclear how MP03-33 fits into the MP03-36 program. MedPointe cannot rely on cross study comparability between MP03-36 and the approved product and MP03-33 and the approved product. The program, as designed, cannot demonstrate that the higher strength is better. MedPointe would need a study that directly compared MP03-33 to MP03-36 to determine if there is an efficacy advantage with MP03-36 compared to MP03-33.

In general, the Division indicated that MedPointe may submit one SAR and one PAR trial in support of both indications, if both trials are adequate and well-controlled Phase 3 trials and both trials support efficacy and safety of the drug.

3. *Since your proposed study in SAR patients will likely involve two primary efficacy comparisons (i.e., each regimen of MP03-36 versus placebo) a correction for multiplicity in the primary efficacy analyses will be needed.*

Discussion:

MedPointe stated that they will submit a statistical analysis plan for review and comment. Med Pointe asked if a step-down procedure (i.e., testing the twice per day regimen versus placebo first followed by a test of the once per day regimen versus placebo only if statistical significance is achieved with the twice per day regimen) would be an acceptable way to correct for multiplicity in the primary efficacy analyses. The Division agreed.

5.0 Question: Pharmacokinetic Requirements

MedPointe proposes to conduct a single dose pharmacokinetic study that will include the current Astelin Nasal Spray, MP03-33 (0.1% azelastine and (b) (4) ***sucralose), and MP03-36 (0.15% azelastine and*** (b) (4) ***sucralose). Three groups of 18 subjects each will receive a single dose of one intranasal azelastine formulation dosed at 2 sprays per***

nostril. Comparative pharmacokinetic measurements (Cmax, Tmax, and AUC) will be assessed. We believe this single dose pharmacokinetic study is sufficient to evaluate pharmacokinetic profile of the higher strength azelastine nasal spray.

Does the Division agree?

FDA Response:

The approach is acceptable. However, an appropriate number of subjects should be enrolled in the study in order to obtain meaningful PK data.

6.0 Question: Toxicology Requirements

MedPointe completed three 2-week nasal irritation studies, (two in rats and one in dogs) for MP03-33 which contains 0.1 % azelastine and (b) (4) ***sucralose. The final reports for these studies were submitted to IN 69,785 on 6/2/05 (Serial No. 009) and 2/13/06 (Serial No. 015). A 6-month nasal irritation study in rats assessing MP03-33 is nearing completion. Based on these studies, MedPointe believes that the rat is the more sensitive species for evaluating intranasal formulations containing azelastine and sucralose.***

MedPointe completed three 2-week nasal irritation studies that include the higher strength formulation: two in rats and one in dogs. The final report for the first rat study was submitted to IND 69,785 on 6/2/05 (Serial No. 009) and draft reports for the dog and second rat study were submitted to this IND on 6/28/06 (Serial No: 021). A 6-month nasal irritation study in rats that includes the higher strength formulation is ongoing. We believe these toxicology studies provide an adequate preclinical database for evaluation of the safety of this higher strength azelastine nasal spray to support the studies outlined in Questions 3 and 4, and that no further long-term studies are necessary.

Does the Division agree?

FDA Response:

Regarding the most sensitive species in evaluating toxicity of MP03-33 and MP03-36, the available evidence is not conclusive to support the assertion that the rat is the most sensitive species in evaluating these intranasal formulations containing azelastine and sucralose. However, it appears reasonable and acceptable to conduct chronic (i.e., 6-months) intranasal toxicity studies evaluating toxicity of the components and formulations in rats.

As for the need for additional toxicity studies to support long-term (i.e., 6 – 12 months in treatment duration) clinical trials of MP03-36, the high strength formulation (0.15% azelastine HCl), we cannot agree at the present time with the assertion that no additional toxicity studies are needed. We defer our decision until the submission and review of the

ongoing 6-month intranasal toxicity study with 0.15% azelastine. Submission of the 6-month study with 0.1% azelastine may also be helpful. In principle, well-designed 6-month intranasal toxicity studies in rats would generally be sufficient to support long term clinical studies if there are sufficient safety margins for the individual formulation components or the new formulation as a whole and there is no treatment-related neoplastic effect.

Of note, the ongoing 6-month intranasal toxicity studies of MP03-33 and MP03-36 in rats would not be considered adequate in characterizing the toxicity of either formulation if their designs are similar or identical to those of the completed 2-week toxicity studies in rats and dogs (i.e., Study Nos. 0437RMS57.002 and 0437RMS57.004) due to the lack of appropriate controls (e.g., saline). Consequently, additional toxicity evaluation will be required if the Division determines that these 6-month studies in rats are inadequate. You are encouraged to submit protocols for comment for any future pivotal toxicity studies.

Discussion:

MedPointe indicated that its representatives in attendance at the meeting do not have the expertise to conduct in depth discussions about the scientific interpretations of their toxicity study results. The current discussions are mainly from a regulatory perspective. Additional discussions on the technical aspects of the studies may be needed when they have their experts present.

MedPointe requested clarification as to whether the Division's response implied that a study in a second species may be needed. MedPointe also provided a handout which outlined their Toxicology program (see attachment).

The Division stated that it was not asking for toxicity studies in an additional animal species. The Division would accept the rat as a valid species to investigate the chronic toxicity of the proposed drug formulation although the available data do not definitively indicate that the rat is more sensitive than the dog. If the Division is concerned about any findings in the completed or future studies, it may ask for additional studies in rats with appropriate study designs to address the concern.

MedPointe also indicated that they did not expect the Division's response that the completed or ongoing toxicity studies of formulation MP03-36 might be considered inadequate. MedPointe believed that their study designs addressed the Division's concerns that were expressed in previous discussions. MedPointe, therefore, believed that these studies should be adequate to qualify the drug formulation as well as the excipients.

The Division stated that MedPointe was previously informed that consultation with the Division regarding study design is encouraged (see May 3, 2005, meeting minutes), but MedPointe elected not to do so. The Division also stated that toxicity studies should be designed to thoroughly evaluate the effect of sucralose and sorbitol on the nasal surface

epithelium and to identify a no-observed-adverse-effect-level (NOAEL) for sucralose. Such studies should employ appropriate controls such as saline that are not expected to cause any significant adverse reactions. Yet the completed 2-week studies in rats and dogs (Studies Nos. 0734RMS57.004 and 0734RMS57.005) did not include an appropriate control group to properly evaluate the effects of sucralose and sorbitol. The studies included only two groups: vehicle (containing sucralose, sorbitol and other ingredients) and vehicle plus 0.15% azelastine. Furthermore, Study 16365 demonstrated that azelastine at concentrations of 0.1% and (b) (4) is slightly irritating to the nasal cavity. The Division noted that while the individual studies were not considered to be adequately designed, the ongoing clinical trials were considered safe to proceed based on an integrated evaluation of all of the nonclinical studies.

The Division's concern regarding the ongoing 6-month studies in rats is related to the inclusion of adequate control groups since MedPointe's meeting package did not provide any details to the study designs. Based on MedPointe's handout at the meeting, the ongoing 6-month study (study number unknown) appears to use the approved azelastine formulation (Astelin Nasal Spray) as the control group. The use of this type of a control group may hinder the ability to evaluate the effects of sucralose and sorbitol and would not allow for identification of a true NOAEL for sucralose. However, this study design may allow for a determination that the presence of sucralose and sorbitol did not enhance the local toxicity of the approved azelastine formulation. The Division will determine the acceptability of the ongoing studies to address the safety issues associated with the proposed azelastine formulation when the 6-month study in rats is submitted. MedPointe and the Division agreed to conduct further discussions if needed regarding qualification of the sucralose and sorbitol as excipients in the to-be-marketed drug products after MedPointe submits the relevant supporting data.

MedPointe asked if they need to qualify the sucralose and sorbitol for the MP03-33 and MP03-36 formulations individually. The Division stated that adequate qualification of these excipients in one formulation would extend to the second formulation. However, bridging toxicity studies with the to-be-marketed formulation may be necessary to address any formulation-related effect.

Minutes Preparer
Colette Jackson

Attachment: MedPointe Handout

New Astelin Products
Toxicology
Tested Formulations (major components)

A. 2-week Study in Rats (Product Safety Labs)

Treatment Groups
1. Vehicle
2. New vehicle (sorbitol and sucralose)
3. Astelin Nasal Spray (marketed product)
4. 0.1% azelastine + (b) (4) sucralose + sorbitol
5. 0.15% azelastine + (b) (4) sucralose + sorbitol

B. 2-week Study in rats, 2-week study in dogs (Calvert

Treatment Groups
1. 0.15% azelastine + (b) (4) sucralose + sorbitol
2. New vehicle (sorbitol and sucralose)

C. 6-month study in rats (Calvert)

Treatment Groups
1. 0.1% azelastine + (b) (4) % sucralose + sorbitol
2. 0.15% azelastine + (b) (4) sucralose + sorbitol
3. Astelin Nasal Spray (marketed product)
4. New Vehicle (sucralose + sobitol)

Drafted by: CCJ/September 19, 2006

Initialed by: Pei/ September 26, 2006
McGovern/ September 26, 2006
Gebert/ September 25, 2006
Davi/ September 25, 2006
Limb/ September 25, 2006
Seymour/ September 25, 2006
Chowdhury/ September 28, 2006

Finalized: CCJ/September 28, 2006

Filename: 69785 August 29 2006 MM

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/s/

Colette Jackson
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