



WRITTEN REQUEST

NDA 202236
NDA 022203

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

Attention: Cindy Yayac, Senior Manager
Regulatory Affairs

Dear Ms. Yayac:

Reference is made to your May 7, 2013, Proposed Pediatric Study Request for Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray, 137 mcg/50 mcg (0.1%/0.037%).

We also refer to Astepro (azelastine hydrochloride) Nasal Spray, 137 mcg and 205.5 mcg (0.1% & 0.15%), and your 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.

BACKGROUND:

These studies will investigate the potential use of a fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray for the treatment of seasonal allergic rhinitis in children 4 to 11 years of age who require treatment with both azelastine hydrochloride and fluticasone propionate. The safety of azelastine hydrochloride nasal spray (0.1% & 0.15%) will also be evaluated in pediatric patients aged 6 months to less than 6 years of age with perennial and/or seasonal allergic rhinitis.

The fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray is the only combination antihistamine and corticosteroid nasal spray approved for the treatment of seasonal allergic rhinitis.

Allergic rhinitis is a highly prevalent disease in both adults and children. While the focus of seasonal allergic rhinitis treatment is the management of symptoms, survey data indicate that the burden of these symptoms is substantial, with effects on both the physical and emotional health of children.¹

This fixed-dose combination nasal spray is comprised of two classes of medications which are instrumental in the management of allergic rhinitis.² As the only combination antihistamine and

¹ Meltzer EO, Blaiss MS, Derebery MJ, et al. Burden of Allergic Rhinitis: Results from the Pediatric Allergies in America Survey. *J Allergy Clin Immunol.* 2009; 124(3 Suppl): S43-70

corticosteroid nasal spray approved for the treatment of seasonal allergic rhinitis, this product offers an additional treatment option for individuals with seasonal allergic rhinitis who require treatment with both azelastine hydrochloride and fluticasone propionate. Children 4 to 11 years of age with seasonal allergic rhinitis who require treatment with more than one agent may also be expected to benefit from the availability of this combination product.

The studies outlined in this Written Request are designed to evaluate the safety of azelastine hydrochloride in pediatric patients aged 6 months to less than 6 years of age and to provide evidence of efficacy and safety for use of this fixed-dose combination product in children 4 to 11 years of age. Study 1 will evaluate the safety of azelastine hydrochloride (Astepro) nasal spray in pediatric patients 6 months to less than 6 years of age with perennial and/or seasonal allergic rhinitis. Study 2 will evaluate the long term safety of the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray in children 4 to 11 years of age with seasonal allergic rhinitis or perennial allergic rhinitis. Study 3 will evaluate the efficacy and safety of this fixed-dose combination in children 4 to 11 years of age with seasonal allergic rhinitis.

Safety concerns with intranasal antihistamines include somnolence and local nasal effects such as epistaxis. Intranasal azelastine hydrochloride is also associated with dysgeusia. Safety concerns with intranasal corticosteroids include local nasal effects such as epistaxis, nasal ulcerations, and nasal septal perforation. Monitoring for safety concerns must be performed in the proposed clinical trials, as described below.

Additional risks associated with the corticosteroid drug class include growth suppression, increased intraocular pressure, glaucoma, cataracts, decreased bone mineral density, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis suppression. These risks have been evaluated in trials previously conducted for fluticasone propionate nasal spray.

To obtain needed pediatric information on azelastine hydrochloride and the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies):*

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Study 1: A randomized, open-label, parallel group, safety study in children 6 months to less than 6 years of age with perennial and/or seasonal allergic rhinitis evaluating azelastine hydrochloride (Astepro) nasal spray. The treatment duration will be 4 weeks.

² Wallace DV, Dykewicz, MS, Bernstein DI, et al. Diagnosis and Management of Rhinitis: An Updated Practice Parameter. *J Allergy Clin Immunol.* 2008;122:S1-S84

Study 2: A randomized, open-label, active-controlled, parallel group, long-term safety study in children 4 to 11 years of age with seasonal allergic rhinitis or perennial allergic rhinitis comparing the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray to fluticasone propionate nasal spray. The treatment duration will be 3 months.

Study 3: A randomized, double-blind, placebo-controlled, parallel group efficacy and safety study in children 4 to 11 years of age with seasonal allergic rhinitis comparing the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray to placebo. The treatment duration will be two weeks.

- *Objective of each study:*

Study 1: To evaluate the safety of azelastine hydrochloride (Astepro) nasal spray in children 6 months to less than 6 years of age with perennial and/or seasonal allergic rhinitis.

Study 2: To evaluate the long-term safety of the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray in children 4 to 11 years of age with seasonal allergic rhinitis or perennial allergic rhinitis.

Study 3: To evaluate the efficacy and safety of the fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray in children 4 to 11 years of age with seasonal allergic rhinitis.

- *Patients to be studied:*

- *Age group in which study(ies) will be performed:*

- *Study 1:* Children 6 months to less than 6 years of age.
- *Study 2:* Children 4 to 11 years of age.
- *Study 3:* Children 4 to 11 years of age.

- *Number of patients to be studied:*

- *Study 1:* Approximately 192 subjects, randomized 1:1 to azelastine hydrochloride (Astepro) 0.15% nasal spray or azelastine hydrochloride (Astepro) 0.1% nasal spray.
- *Study 2:* Approximately 400 subjects, randomized 3:1 to the fixed-dose combination of azelastine hydrochloride and fluticasone propionate nasal spray or fluticasone propionate nasal spray.
- *Study 3:* Approximately 350 subjects, randomized 1:1 to the fixed-dose combination of azelastine hydrochloride and fluticasone propionate nasal spray or placebo.

Representation of ethnic and racial minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial

minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

Study 1: Safety endpoints must include adverse events, vital signs, laboratory parameters, and nasal examinations.

Study 2: Safety endpoints must include adverse events, vital signs, laboratory parameters, and nasal examinations.

Study 3: The primary efficacy endpoint will be the change from baseline in the AM+PM 12-hour reflective Total Nasal Symptom Score (rTNSS) for the entire double-blind period. Safety endpoints must include adverse events, vital signs, and nasal examinations.

- *Known drug safety concerns and monitoring:*

Safety concerns with intranasal antihistamines include somnolence and local nasal effects such as epistaxis. Intranasal azelastine hydrochloride is also associated with dysgeusia. Safety concerns with intranasal corticosteroids include local nasal effects such as epistaxis, nasal ulcerations, and nasal septal perforation. Monitoring for safety concerns must be performed in the clinical trials, as listed under the Study Endpoints section above.

As described in the Background Section, additional risks associated with the corticosteroid drug class include growth suppression, increased intraocular pressure, glaucoma, cataracts, decreased bone mineral density, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis suppression. These risks have been evaluated in trials previously conducted for fluticasone propionate nasal spray.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *dosage form:*

- *Study 1:*

- *Astepro 0.1%:* nasal spray containing 137 mcg of azelastine hydrochloride in each 0.137 mL spray
- *Astepro 0.15%:* nasal spray containing 205.5 mcg azelastine hydrochloride in each 0.137 mL spray

- *Studies 2 and 3:* nasal spray containing 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137 mcg/50 mcg) in each 0.137 mL spray
- *route of administration:* nasal inhalation
- *regimen:* 1 spray per nostril twice daily

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

- 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
- 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
- 3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*
Safety data in Study 1 and Study 2 will be summarized by descriptive statistics. Study 3 must have a pre-specified, detailed statistical analysis plan appropriate to the study design and outcome measure. The statistical analysis plan for Study 3 should be submitted prior to the start of the study. This should include information addressing the issue of missing data, clearly specifying an estimand and any associated data imputations that may be required for the

key efficacy endpoint. Reasons for discontinuation of treatment or withdrawal from the study should be recorded, avoiding less informative terms such as ‘lost to follow-up’, ‘patient/investigator decision,’ ‘withdraw consent’, in favor of categories relevant to safety or effectiveness, such as ‘treatment ineffective’ or ‘adverse reaction.’ You should refer to “The Prevention and Treatment of Missing Data in Clinical Trials” by the National Research Council³.

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that a fixed-dose combination of azelastine hydrochloride and fluticasone propionate in a nasal spray is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).
- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain Agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical*

³ Panel on Handling Missing Data in Clinical Trials: National Research Council; The Prevention and Treatment of Missing Data in Clinical Trials; The National Academies Press; 2010.

Product Applications and Related Submissions Using the eCTD Specifications at <http://www.fda.gov/Cder/guidance/7087rev.htm>.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before September 30, 2014. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.
- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or

4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Philantha Montgomery Bowen, Senior Regulatory Management Officer, at 301-796-2466.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

CURTIS J ROSEBRAUGH
09/06/2013