



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

Memorandum of Facsimile Correspondence

Date: May 19, 2008

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

Company: Meda Pharmaceuticals

Fax: 732-564-2361

Phone: 732-564-2358

From: Philantha Bowen, MPH, RN
Senior Regulatory Management Officer
Division of Pulmonary and Allergy Products

Subject: IND 77363; Re: SPA Meeting Minutes

of Pages including cover: 10

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Thank you.

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SUBJECT TO STIPULATED PROTECTIVE ORDER

MEDA_APTX03071217

CIP2165
Argentum Pharmaceuticals v. Cipla Ltd.
IPR2017-00807
PTX0114-00001



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type: Type A
Meeting Category: Special Protocol Assessment
Meeting Date and Time: April 29, 2008 9:00-10:00 AM
Meeting Location: Building 22, Conference Room 1415
Application Number: IND 77,363
Product Name: Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray
Received Briefing Package: April 15, 2008
Sponsor Name: MEDA Pharmaceuticals
Meeting Requestor: Richard Fosko, R.Ph., MPH
Director, Regulatory Affairs
Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D., Director
Division of Pulmonary and Allergy Products
Meeting Recorder: Philantha M. Bowen, MPH, R.N.
Sr. Regulatory Management Officer
Meeting Attendees:

FDA Attendees

Office of Drug Evaluation II

Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary and Allergy Products

Philantha Bowen, M.P.H., RN, Sr. Regulatory Management Officer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D., Clinical Team Leader, Division of Pulmonary and Allergy Products

C. Joe Sun, Ph.D., Pharmacology/Toxicology Team Leader, Division of Pulmonary and Allergy Products

Jean Wu, M.D., Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products

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Office of New Drug Quality Assessment

Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment I, Branch II

Eugenia Nashed, Ph.D., Quality Reviewer, Division of Pre-Marketing Assessment I, Branch II

Office of Clinical Pharmacology

Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 2

Sponsor Attendees

Richard Spivey, PharmD, Ph.D., Senior Vice President, Research and Development

Harry Sacks, M.D., Vice President, Medical and Scientific Affairs

Cary Sax, Associate Director, Regulatory Affairs

Warner Carr, MD, Consultant

Phillip Lieberman, MD, Consultant

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1.0 BACKGROUND

MEDA Pharmaceuticals submitted a Special Protocol Assessment (SPA) dated December 21, 2007, for the clinical protocol MP4002 for the azelastine/fluticasone combination nasal spray. On January 31, 2008, the Division responded to MEDA's SPA request.

MEDA Pharmaceuticals submitted a Type A meeting request, dated February 29, 2008, to discuss the Agency's comments and responses regarding the SPA. The briefing package, dated April 14, 2008, was reviewed by the Division. On April 28, 2008, the Division responded to MEDA's questions via facsimile. The content of the fax is printed below.

Any discussion that took place at the meeting is captured in section 3.0 including any changes in our original position. MEDA's questions are in ***bold italics*** and FDA's response is in *italics*; the discussion is in normal font.

2.0 QUESTIONS

2.1 QUESTION 1

Question 1:

Does the Division agree that patients with moderate/severe nasal symptoms of seasonal allergic rhinitis, as defined by ARIA, is an appropriate target population for this drug?

Division Response:

We do not agree. We have expressed concerns that you have not provided evidence that a population for this combination product exists. The ARIA Guidelines presented do not alleviate these concerns. The ARIA classification for allergic rhinitis classifies allergic rhinitis based upon intermittent and persistent symptoms and is not universally adopted in the United States. In particular, this type of classification is not used for approval of therapeutics for allergic rhinitis.

The combining of different products to control symptoms of SAR is the practice of medicine. Single ingredient products containing azelastine or fluticasone propionate are approved for treatment of symptoms of seasonal allergic rhinitis. The combination product that you are proposing to develop is targeted to treat the same symptoms that the single ingredient products are already indicated for. Demonstrating significantly greater symptom relief with the combination product over its individual single active ingredients will not be sufficient to demonstrate that both azelastine and fluticasone propionate contribute to the effectiveness of the combination. Demonstration of greater symptom relief with the combination product over its active ingredients (for the exact same symptoms) is likely to be due to the fact some patients may not be responding to

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azelastine while responding to fluticasone propionate, and vice versa. Rationale based on pharmacodynamic reasoning, such as mechanism of action, onset of symptom relief, etc., are also not sufficient to justify this combination product.

As stated before, combining products eliminates flexibility with dosage titration and potentially exposes patients to unnecessary medication; and thus unnecessary risk.

2.2 QUESTION 2

Question 2:

Does the Division agree that our proposed inclusion/exclusion criteria will study a population of patients with moderate/severe rhinitis?

Division Response:

We do not agree. We do not have specific criteria using the TNSS to define what constitutes moderate or severe allergic rhinitis.

2.3 QUESTION 3

Question 3:

Does the Division agree that the proposed dosage of the individual components of the fixed dosage product (that are within the labeling for those marketed products) is appropriate for study in the MP4002 study?

Division Response:

We remain concerned about the lack of flexibility of dosage titration with the fixed dose combination (FDC). We acknowledge your explanation and ask you to make the reasoning in the NDA, if you are to develop this product. This will be a review issue.

2.4 QUESTION 4

Question 4:

Does the Division agree that no new corticosteroid-specific safety issues are anticipated with the fixed dose combination product that would require MEDA to study a dosage that is lower than the recommended dosage in the fluticasone label? This question is predicated on the assumption that adequate pK studies do not show

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an appreciable enhancement of absorption of fluticasone. In addition, it assumes that appropriate long term studies support the safety of the combination product.

Division Response:

We cannot agree. Your question is based upon assumptions that are unknown at this time. Your FDC, as well as, the individual monotherapies, with new formulations represent new products. The safety and efficacy of each of these products have not been established. Therefore, we cannot agree that no new corticosteroid safety issues are anticipated.

2.5 QUESTION 5

Question 5:

If the Division still does not agree that we have appropriately applied the specific elements of the combination rule stated above, then we respectfully request the opinion of the Director of the Office of Drug Evaluation II on the above issues. In addition, we would also request input from the Office of Medical Policy on the Division's interpretation of these elements of the combination rule under these circumstances.

We believe we have addressed your questions adequately and the responses can be discussed at the face-to-face meeting.

ADDITIONAL COMMENT: CMC

We note that four new suspension nasal spray drug products were manufactured for the use in this IND, i.e., azelastine hydrochloride/fluticasone propionate combination nasal spray (different formulation from the original IND submission), two single-active-comparator nasal sprays, and a placebo nasal spray. Any further development in the clinical program must be accompanied by the submission of the formal in vitro characterization studies for these drug products, as described in our Guidance "Nasal Spray and Inhalation Solution, Suspension, and Drug Products". In particular, provide the dose performance data (e.g., emitted dose, spray content uniformity, droplet size distribution, etc.) that characterizes the combination nasal spray product and the two monotherapy products (azelastine hydrochloride nasal spray and fluticasone propionate nasal spray). Provide these data in a side-by-side presentation using graphs, in order to demonstrate the pharmaceutical comparability of the in vitro dose delivery for the single component drugs relative to the combination product.

3.0 DISCUSSION

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MEDA began the discussion seeking clarification on an appropriate patient population and a better understanding of application of the combination product rule. MEDA outlined the following points for clarification:

- An understanding of the Division's position of why it is a problem that the proposed combination product is targeted to treat the same symptoms as the single product ingredients;
- An explanation as to why the combination product, if shown to demonstrate greater symptom relief over the single ingredients, is not sufficient;
- Discussion and clarity of the Division's position that greater symptom relief with the combination product over the active ingredients may be a result of some patients responding to one single ingredient over the other.

MEDA informed the Division that the rationale for the combination product was based upon input from allergists who noted they treat many of their SAR patients with both azelastine and fluticasone nasal sprays. MEDA acknowledged the Division's comment that combining different products to control symptoms of SAR is the practice of medicine. However, MEDA explained that the combination product would be better than the individual ingredients because patients would not have to take four sprays of medication at a time. With the individual components, compliance becomes an issue; thus leading to treatment failures and unmet patient needs. MEDA suggested that the patient population would be those who have failed common treatments regimens and those who would be inconvenienced by taking two single drug products. In terms of safety, MEDA commented that combining the two products versus the individual components would not alter the safety. In fact, the product will be effective and pose less of a risk. MEDA cited examples of other combination products that also treated the same disease, e.g. LABA and ICS for asthma. MEDA asked the Division to provide its expectation of efficacy for the combination product.

The Division responded that the combining of two drugs to treat the same symptoms of a disease is problematic. The Division noted that the combination of azelastine and fluticasone nasal spray is approved as Duonase in India. The Division or MEDA's consultants did not know the specific background of the premise of Duonase approval in India. The Division mentioned that at a recent meeting (AAAAI 2008) where one of the MEDA consultants Dr. P. Lieberman spoke at an academic session, a comment was made from the audience that suggested that the premise of this combination product is that it treats two different types of rhinitis: allergic and non-allergic. The Division commented that such a premise would seem reasonable. The Division noted that MEDA proposes the combination product for the same indication, symptoms of SAR. While the proposed combination may be a choice in the practice of medicine, it is not necessarily rationale as a fixed dose combination. If we look at the cough, cold, allergy, bronchodilator, and antihistamine drugs OTC monograph (21 CFR 341), permitted combinations are described. The combinations described include components that treat a different aspect of the disease, e.g. antihistamine and decongestant or antihistamine and antitussive. The

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monograph does not allow combination of two drugs that treat the same aspect of the disease, e.g. antihistamine and antihistamine.

The next issue is the combination rule, i.e. that each component makes a contribution to the claimed effects. With the proposed program, MEDA would use the same endpoint, total nasal symptom score (TNSS), to evaluate the efficacy of the combination product and each component. This is problematic because some patients may not respond to one component, but yet respond to the combination; and use of the same endpoint will not discriminate. For example, if a patient has failed azelastine therapy, but responds to the combination product, then it could imply that the response is toward the effects of the steroid; however the patient would receive the combination product where one component provides no benefit, but yet exposes them to unnecessary risk. In addition, the Division raised the possible safety concern regarding the lack of flexibility for dosage titration for the proposed combination product.

MEDA responded that patient response to the combination can be viewed as a synergistic effect. In terms of treatment failure, MEDA stated that "treatment failure" could mean that patients failed to get complete symptom relief. Moreover, MEDA pointed out that for any combination product it may be difficult to determine which component is providing the benefit; hence, randomized studies are used. MEDA questioned the Division as to why this approach could not be utilized with the proposed product. The Division addressed the combination product referenced, LABA and ICS, which have different endpoints to measure disease benefit. In MEDA's proposed program, however, the endpoints are the same and the product is aimed at treating the same aspects of the disease with the two drugs. With such a design, the Division reiterated that it is difficult to determine the contribution of each component.

MEDA noted that there are approved combination products that have the same endpoints (e.g. analgesics); and questioned the application of the combination rule in this situation. The Division could not comment on the application of the combination rule for those particular situations. MEDA was informed of the recent regulatory action taken on a combination product that addressed benefit on the same aspects of disease. The Division stated that it would be MEDA's choice on whether to pursue the study using the same endpoints to measure disease benefit, but MEDA should understand the Division's concerns.

MEDA asked whether other endpoints, such as onset of action, may address the Division's concerns. The Division did not think that onset of action will demonstrate the expected outcome. The Division responded that different methods are risky, however, innovation is encouraged.

The Division, acknowledged MEDA's request to have clarification of the combination rule, and informed MEDA of three aspects to be considered for combination products:

- CFR 341.50 outlines the lists of monographs for combination products that are permitted by law. In addition, the appropriate language for the label is provided, as well as, separate indications for each of the drug components. As discussed

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earlier, this approach does not provide for combining products that treat the same aspect of the disease. The rationale outlined in CFR 341.50 is sensible, and there is no reason that the same rationale would not apply for prescription products.

- Per CFR 300.50 each component has to make a contribution to the claimed effect. As discussed earlier, the Division stated that it will be difficult to determine the contribution of each component for MEDA's combination product.
- Per CFR 300.50, special cases are allowed if a component is added to enhance the safety or effectiveness of the principle active component. MEDA's combination product does not fit this special case.

MEDA commented that for some combination products, i.e. analgesics, have the same endpoints and the individuals components of the product, as well as the combination, have been superior to placebo. MEDA does not understand how the combination rule precludes development of their combination product. MEDA verbalized their disagreement with Division's position and commented that the pathway for their proposed product for allergic rhinitis is halted.

The Division informed MEDA that consultation and collaboration had been sought with other offices in the Agency, therefore the position taken had not been in isolation. The pathway forward may be for MEDA to formally dispute the Division. The dispute process may be a way to seek the direct involvement of the Office Director. At this point, it will be MEDA's choice to pursue the clinical development program. The Division commented that there appears to be no safety risk in MEDA conducting the study.

The Division recommended to MEDA that if product development is pursued, the CMC information (performance in terms of emitted dose and droplet size distribution) must be evaluated and addressed carefully and referred MEDA to the CMC additional comment provided in the Division's responses. In addition, since each monotherapy represents a new product, one API is in solution (azelastine nasal spray) and the other API is a suspension (fluticasone nasal spray), it was recommended that MEDA address these differences in a side-by-side comparison format.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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Linked Applications

Sponsor Name

Drug Name

IND 77363

MEDA
PHARMACEUTICALS
MEDA
PHARMACEUTICALS
INCAZELASTINE/FLUTICASONE
COMBINATION NASAL

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/s/

PHILANTHA M BOWEN
05/19/2008

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