



**Food and Drug Administration
Center for Drug Evaluation and Research**

I. Office of Drug Evaluation II

Memorandum of Facsimile Correspondence

Date: September 7, 2007

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Subject: IND 77363; Re: 10 Sept 07 Meeting Q & A

of Pages:

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Thank you.

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Argentum Pharmaceuticals v. Cipla Ltd.

IPR2017-00807

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IND 77,363

AzelaStine-Fluticasone

MedPointe Pharmaceuticals

Attached are the FDA responses to the questions (in bold italics) in your July 31, 2007, meeting package regarding azelaStine/fluticasone. You have the option of canceling our meeting on September 10, 2007, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions for which you would like FDA feedback should be submitted as a new meeting request.

Please let me know as soon as possible if you would like to cancel the meeting or change it to a teleconference.

Introductory comment

According to 21CFR300.50, two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects. Your development program should demonstrate the efficacy and safety of the fixed-combination drug and the contribution of each component to the combination. Determination of the appropriate comparator monotherapy treatment arms for the pivotal studies is critical to your development program. One option would be to develop monotherapies that are essentially the combination product minus one of the active ingredients. This may minimize the pharmaceutical differences between the combination product and the monotherapy components. However, as you note, one potential problem is that removal of an active drug substance from your combination product may change the properties of the monotherapy. This complicates your development program and may be difficult to address.

You propose the following monotherapy comparators, Flonase Nasal Spray and Astelin nasal spray. As stated previously, there are pharmaceutical differences between your combination product and your proposed monotherapy comparators which may significantly impact efficacy and safety, complicating interpretation of clinical trial results. If you wish to pursue using these marketed products as the monotherapies in the pivotal studies, you would need to adequately demonstrate the comparability of fluticasone delivered as Flonase and fluticasone delivered via your combination product, as well as, the comparability of azelaStine delivered as Astelin and azelaStine delivered via your combination product. Demonstration of comparability is quite a high hurdle and would include in vitro, pharmacokinetic, and pharmacodynamic data. Because of the pharmaceutical differences and lack of an objective pharmacodynamic endpoint for allergic rhinitis, demonstration of comparability is likely not feasible. Furthermore, blinding of such commercial comparators in pivotal studies would be problematic due to

differences in the delivery systems. Incorporating appropriate dummy products for blinding would introduce additional issues regarding spray volumes. Thus, we do not see a path forward for using Flonase and Astelin as the comparator monotherapies.

In addition, according to 21CFR300.50, the combination should be safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Therefore, you need to identify a patient population that requires such a combination product. Your clinical development program should evaluate the proposed combination product in the proposed patient population that requires concurrent therapy with both azelastine and fluticasone propionate. Identification of such a patient population may be a challenge for your development program.

Question 1:

We plan to demonstrate the clinical efficacy and safety of our proposed combination drug product through two pivotal comparative, placebo-controlled clinical trials and to demonstrate clinical safety in an additional 12-month trial, as proposed in our IND. The proposed safety study should provide adequate data to determine the safety of the proposed formulation, delivery device, and dosing schedule. Considered along with the proposed toxicology program (IND 77-363 initial submission), does the Division agree that safety issues are adequately addressed.

Division response: The proposed safety program (two pivotal placebo-controlled trials and a 12 month clinical safety trial) appears reasonable, assuming selection of appropriate monotherapy comparators in the pivotal studies as discussed in the introductory comment. However, additional safety data may be required depending on the adverse event profile and systemic exposure observed for the proposed combination drug product.

Question 2:

Does the Division agree that Flonase is an appropriate control for the proposed 12-month clinical safety trial?

Division response: No, we do not agree. While inclusion of an active comparator such as Flonase or Astelin is your choice, the proposed 12-month safety trial should include a placebo treatment group.

Question 3:

We are proposing a drug/drug combination product that, based on our proof of concept study (MP428), may have significant clinical advantages over the commercially available monotherapies. Our proposed clinical program includes a vehicle placebo control, thus providing comparison to the potential effects of the excipients without drug actives. Combining a soluble and an insoluble API in a single nasal spray formulation presents unique issues, rendering this an atypical

situation that requires careful consideration. Does the Division agree that this proposed combination product is atypical and as such may require an alternative approach that will also satisfy the combination product rule?

Division response: We agree that your combination product poses some unique issues that may be difficult to address. However, this does not change our interpretation of what is necessary to satisfy the combination product rule.

We note that you propose your combination product will have significant advantages over commercially available monotherapies. If you intend to pursue a superiority claim, we recommend you discuss the feasibility of such a claim with the Agency.

Also, we note a potential disadvantage of the proposed combination over the commercially available monotherapies. For example, a fixed-dose combination does not allow the downward dose titration or as needed administration of fluticasone propionate, which are options with the commercially available monotherapy.

Question 4:

Formulating monotherapy comparators with identical formulations to the proposed combination product but without one or the other of the APIs may result in changes to the formulation that render the monotherapies unsuitable for the proposed use. For example, removing fluticasone may change the viscosity and/or spray pattern, droplet size, or plume geometry of the Division proposed azelastine monotherapy comparator when compared to the combination formulation. Similarly, removing azelastine may cause changes. Thus, the monotherapies proposed by the Division may demonstrate differences between these monotherapies and the proposed combination product and thus not be consistent with the Division's intent when proposing these monotherapies. Does the Division agree?

Division response: As stated in the introductory comment, we acknowledge the potential for your monotherapy product to be affected by removal of one of the APIs. This could complicate your development program and may be difficult to address.

Question 5:

The proposed combination product cannot use the same nasal spray device as each approved monotherapy because Astelin and Flonase use different metered spray pumps. Using the proposed combination product spray pump with the Division's recommended, specially formulated monotherapy comparators may affect the efficacy of the monotherapy comparators as compared to the approved monotherapies. Using the approved monotherapies assures the comparators will have the efficacy and safety physicians associate with these products.

- a. Does the Division agree that the use of specially formulated monotherapy comparators with a spray pump designed for use with the proposed combination product may alter the known efficacy of the monotherapies?
- b. Does the Division agree that using the monotherapies proposed by the Division with the proposed combination product spray pump may not meet the Division's intent in proposing the use of these specially formulated monotherapies?

Division response: Refer to the introductory comment and response to Question 4.

Question 6:

The use of specially formulated monotherapies for comparator controls in pivotal clinical trials provides comparator data that are only directly applicable to the specially formulated monotherapy comparators and may not reflect either the efficacy or safety of the approved monotherapies. Data derived from the use of these specially formulated monotherapies will not provide prescribing physicians usable information about the approved commercial monotherapies compared to the proposed combination product to assist in their prescribing decisions. We believe the use of the approved monotherapies will provide physicians the information they need to assess the value of the proposed combination.

- c. Does the Division agree?
- d. If not, can the Division expand upon their position and how the results of the studies using the specially formulated comparators would be explained in the package insert and provide usable information for the physician?

Division response: c) We do not agree. Refer to the introductory comment. The fixed-combination drug regulations do not stipulate that clinical trials establish a comparison with commercially available monotherapies. d) For an example of a description of clinical studies to support approval of a combination product, we refer you to the Symbicort Inhalation Aerosol product label.

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/s/

Philantha M Bowen
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CSO

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