CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022383 **COMPLETE RESPONSE**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your new drug application (NDA) dated December 15, 2008, received December 18, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Arcapta Neohaler (indacaterol maleate inhalation powder), 150/300 mcg per capsule.

We acknowledge receipt of your amendments dated January 15, March 19 and 31, April 2, 3, 8, 15, 17, 28, and 30, May 20, June 9, 18, and 26, July 15, and August 6, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and our recommendations to address these issues.

CLINICAL

1. The submitted data do not provide substantial evidence of safety to support the use of Arcapta Neohaler at the proposed doses of 150 mcg and 300 mcg once daily in patients with chronic obstructive pulmonary disease (COPD). At the proposed doses, there were unacceptable higher frequencies of cardiovascular and cerebrovascular serious adverse events compared to placebo and to formoterol in patients with COPD, and possible asthma-related deaths compared to salmeterol in patients with asthma.

2. The submitted studies do not show a clinically meaningful efficacy difference between the 75 mcg once daily dose compared to the 150 mcg or 300 mcg once daily doses or the 150 mcg dose compared to the 300 mcg dose.

3. An appropriate dosing frequency has not been explored in clinical studies.

4. The submitted data do not provide substantial evidence to support use of two different doses in patients with COPD. The data submitted did not show a clinically meaningful advantage of 300 mcg dose over 150 mcg dose, especially in regards to potential safety disadvantages associated with the administration of a higher dose.

To support approval of indacaterol in COPD patients, conduct clinical studies to explore efficacy and establish the safety of doses lower than the proposed 150 mcg dose and to study various dosing frequencies to support your proposed dosing frequency.

To support approval of two doses of indacaterol in COPD patients, provide replicate data showing clinically meaningful advantage of a higher dose compared to a lower dose, and balancing safety data to show no unacceptable safety disadvantage with the higher dose.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Arcapta Neohaler (indacaterol maleate) to ensure that the benefits of the drug outweigh the risk of asthma-related death. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

> **Medication Guide**: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Arcapta Neohaler (indacaterol maleate) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Arcapta Neohaler (indacaterol maleate). FDA has determined that Arcapta Neohaler (indacaterol maleate) is a product that has a serious risk (relative to benefits) in patients with asthma of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use, Arcapta Neohaler (indacaterol maleate).
>
> Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Arcapta Neohaler (indacaterol maleate).
>
> **Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of

submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31 should conclude no earlier than June 1.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Arcapta Neohaler (indacaterol maleate). Additionally, all relevant proposed REMS materials should be appended to the proposed REMS. Once FDA finds the content of the REMS acceptable and determines that the application can be approved, we will include this document as attachments to the approval letter that includes the REMS.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

Your assessment of the REMS should include an evaluation of patients' understanding of the serious risks of Arcapta Neohaler (indacaterol maleate).

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked-up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient."

  or
- "Dispense the accompanying Medication Guide to each patient."

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022383
PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022383
PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send five copies of your REMS-related submissions.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

OTHER

We have the following recommendation:

> The drug target gene, ADRB2, has functional polymorphisms that affect β_2-agonist responses. In addition, indacaterol maleate may be metabolized by CYP3A5, which is also genetically polymorphic. You should explore exposure and response according to ADRB2 and CYP3A5 genotype using previously collected DNA samples to assess their contribution to response variability.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

We note that a post-action feedback meeting to discuss the quality of the application and to evaluate the communication process has been scheduled for November 12, 2009. Please bring your completed Quality Assessment forms to the meeting for reference. This meeting is not considered a PDUFA meeting and minutes will not be generated by FDA.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
REMS Template (Appendices A and B)

APPENDIX A: MEDICATION GUIDE REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31 should conclude no earlier than June 1.

APPENDIX B: REMS SUPPORTING DOCUMENT TEMPLATE

REMS Supporting Document

This REMS Supporting Document should include the following listed sections 1 through 6. Include in section 4 the reason that the Medication Guide proposed to be included in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents

2. Background

3. Goals

4. Supporting Information on Proposed REMS Elements

    a. Medication Guide

    b. Time table for Submission of Assessments of the REMS (for products approved under and NDA or BLA)

5. REMS Assessment Plan (for products approved under a NDA or BLA)

6. Other Relevant Information

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22383	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Arcapta Neohaler

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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
10/16/2009