CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

FINAL REMS REVIEW

Date:	July 1, 2011
To:	Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Through:	Claudia Karwoski, Pharm. D., Director, Division of Risk Management (DRISK)
From:	Kendra Worthy, Pharm.D., Team Leader **DRISK Review Team:** **Scientific Lead:** Yasmin Choudhry, M.D., Risk Management Analyst, Jodi Duckhorn, M.A., Social Science Reviewer
Subject:	Addendum to Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name	Arcapta Neohaler (indacaterol maleate) Inhalation Powder
Indication:	For the treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema in adults
Therapeutic Class:	Long-acting beta$_2$-adrenergic agonist
Application Type / Number:	NDA 22383
Applicant:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2010-2224

This is an addendum to the review of Novartis Pharmaceuticals Corporation's proposed Risk Evaluation and Mitigation Strategy (REMS) for Arcapta Neohaler (indacaterol maleate) NDA 22383, submitted September 28, 2010 (with subsequent revisions). The sponsor's submission received on June 23, 2011, is the subject of this review.

The sponsor proposed changes to the REMS in a June 23, 2011 submission based upon last minute labeling changes, specifically to the boxed warning. The verbiage of the Dear Healthcare Professional and Dear Medical Society Letters was updated to reflect the labeling changes. In final communications, the sponsor was requested to add the proper heading information (REMS approval date and sponsor address) to the REMS document, as it was omitted. The sponsor communicated those changes in a June 30, 2011 communication. DRISK finds the changes acceptable.

See the following appendices:

- Appendix A: Arcapta REMS document
- Appendix B: Arcapta Dear Healthcare Professional Letter
- Appendix C: Arcapta Dear Medical Society Letter
- Appendix D: Arcapta Printed/Web-based materials

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KENDRA C WORTHY
07/01/2011

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP)

NDA #:	NDA # 22-383/ 001 & 002
Products:	Arcapta Neohaler (indacaterol maleate inhalation powder)
APPLICANT:	Novartis
FROM:	Sally Seymour, Deputy Director for Safety, DPARP
DATE:	July 1, 2011

A REMS for Arcapta Neohaler (indacaterol maleate inhalation powder) was submitted on January 18, 2008. In the October 16, 2009, Complete Response letter, the applicant was notified that a REMS for Arcapta Neohaler (indacaterol maleate inhalation powder) was necessary to ensure the benefits of the drug outweighed the risks of asthma related deaths. The REMS elements included a Medication Guide and a timetable for submission of assessments of the REMS.

On February 18, 2010, we notified the applicant that the REMS for the long-acting beta agonists (LABAs), of which Arcapta Neohaler (indacaterol maleate inhalation powder) is a member, would require a communication plan in addition to the Medication Guide and timetable for submission of assessments. This REMS was required to ensure the benefits of the drug outweighed the risks of asthma related deaths. On September 28, 2010, Novartis submitted a proposed REMS for Arcapta Neohaler (indacaterol maleate inhalation powder) that included a Medication Guide, communication plan, and timetable for submission of assessments of the REMS.

The February 25, 2011 draft Guidance for Industry *Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* states that the FDA may approve a Medication Guide under 21 CFR 208 without requiring the Medication Guide to be a part of a REMS when the Medication Guide is adequate to address the serious and significant public health concern and meets the standard set forth under that regulation.

On March 14, 2011, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) met with the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE), to discuss the REMS for the LABAs. The team discussed whether the Medication Guides could be removed from the REMS. DPARP and OSE noted that the main focus of the REMS (MG and CP) for the LABAs was the recent labeling changes with the LABAs, which were geared to the healthcare professional. After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that including the Medication Guide in the REMS for Arcapta Neohaler (indacaterol maleate inhalation powder) is not necessary to ensure the benefits of the drug outweigh the risks described above because labeling will be adequate to address the serious and significant public health concern and meet the standard in 21 CFR 208.1. The Medication Guide will be part of the

approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

The REMS will consist of a communication plan and timetable for submission of assessments of REMS.

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

/s/

CAROL F HILL
07/01/2011

CURTIS J ROSEBRAUGH
07/01/2011

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

FINAL REMS REVIEW

Date:	June 16, 2011
To:	Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Through:	Claudia Karwoski, Pharm. D., Director, Division of Risk Management (DRISK)
From:	**Scientific Lead:** Yasmin Choudhry, M.D., Risk Management Analyst, DRISK **DRISK Review Team:** Jodi Duckhorn, M.A., Social Science Reviewer Kendra Worthy, Pharm.D., Team Leader
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name	Arcapta Neohaler (indacaterol maleate) Inhalation Powder
Indication:	For the treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema in adults
Therapeutic Class:	Long-acting beta$_2$-adrenergic agonist
Application Type / Number:	NDA 22383
Applicant:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2010-2224

1. INTRODUCTION

This is a review of Novartis Pharmaceuticals Corporation's proposed Risk Evaluation and Mitigation Strategy (REMS) for Arcapta Neohaler (indacaterol maleate) NDA 22383, submitted September 28, 2010 (with subsequent revisions). The sponsor's final submission, received on June 10, 2011, is the subject of this review.

2. BACKGROUND

Regulatory History

Arcapta (indacaterol maleate) Neohaler 75 mcg is indicated for once daily treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. Indacaterol is a new molecular entity in the $beta_2$-adrenergic agonist class. Arcapta Neohaler is a dry powder for inhalation available in hard gelatin capsules designed to use with the Neohaler device.

The sponsor's original submission dated December 17, 2008 included proposed once daily dosages of 150 mcg and 300 mcg for Arcapta Neohaler that were associated with serious adverse events, including cardiovascular events, cerebrovascular events, and asthma-related deaths. The Agency issued a Complete Response (CR) letter to Novartis on October 16, 2009, for safety concerns (cardiovascular, cerebrovascular, and asthma-related deaths at the proposed doses) and efficacy concerns (no clinically meaningful efficacy difference demonstrated between the doses studied).The CR letter also specified that a REMS (with a Medication Guide and Timetable for Submission of Assessments) will be required in order to ensure that benefits of the drug outweigh the risks.

The sponsor's submission in response to the CR letter dated September 28, 2010, included a dose response evaluation and dose regimen studies with proposed dosing of 75 mcg and 150 mcg once daily. A Pulmonary, Allergy Drugs Advisory Committee (PADAC) was held on March 8, 2011. The committee members recommended approval of indacaterol 75 mcg (once daily dose) in the maintenance treatment of COPD based on the evidence from 6 adequate and well controlled clinical trials, and the safety profile of the 75 mcg dosage.

Relevant REMS Background

On February 18, 2010, FDA issued a prior approval supplement request for the approved LABAs notifying sponsors of FDA's determination of new safety information of asthma related deaths, intubations, and hospitalizations with the use of the class of long-acting $beta_2$-adrenergic agonists (LABAS). The new safety information about LABAs was based on the Salmeterol Multi-Center Asthma Research Trial (SMART)[1] and the clinical trial data presented as a meta-analysis at the December 2008 joint meeting of the Pulmonary

[1] Nelson HS, Weiss ST, Bleecher ER, et al. The Salmeterol Multicenter Asthma Research Trial. Chest 2006; 129: 15-26.

Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees[2]. The sponsors of approved LABAs were required to submit a proposed REMS for their LABA products to ensure the benefits outweigh the risks. The proposed REMS included a communication plan in addition to the Medication Guide and the timetable for submission of assessments. The sponsor included a proposed REMS in their CR submission that included the required elements.

DRISK reviewed the proposed REMS and had comments (Set #1) dated March 14, 2011 that specifically addressed the following:

- Revision of the goals
- Submission of the actual web-based educational materials
- Expanding the list of professional societies/prescribers
- Revision of the timetable for assessments
- The REMS assessment plan
- Updating the REMS supporting document to be consistent with the REMS document/materials

DRISK also recommended that the content of the printed or web-based material must include at a minimum the following:

- Information about the risk
- Key data regarding the risk (e.g. SMART, SNS)
- New prescribing guidelines
- Currently available LABAs and approved uses
- Prescribing information for Arcapta Neohaler
- Patient Counseling Information
- Questions and Answers
- DHCP Letter (for a period of 1 year)

We also told the Sponsor that some optional pieces could include:

- Resource list of future meetings and peer reviewed journal articles related to LABAs
- Links to FDA Alert(s) for the LABAs

DRISK subsequently reviewed the REMS amendment and comments (Set #2) sent June 7, 2011 addressed:

- The boxed warning and the prescribing guidelines to be consistent with the Arcapta label and the approved LABAs for the proposed indication.
  - The following prescribing guideline for the Class LABA was excluded by the Sponsor "All LABA, including Arcapta Neohaler, are contraindicated in patients with asthma without use of a long-term asthma control."

[2] Presentation of Dr. Andrew Mosholder at the Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee. 10-11 December 2008. See Day One Transcript at pages 149-179.

- Ensuring that the Patient Counseling section of the Printed/Web-based materials mirrors that of the Class LABA Printed/Web-based materials.
- Removing the following sentence from the REMS document: (b) (4) and replacing with: "from the approval of the REMS"
- Editorial track changes to the REMS document and the attached materials.

On Friday, February 25, 2011, FDA published a draft Guidance that addresses when a Medication Guide will be required as part of a REMS. Based on the risks of a drug and public health concerns, FDA has the authority to determine whether a Medication Guide should be required as part of a REMS or should be required as labeling but not part of a REMS. Following the issuance of draft, DRISK and DPARP determined that the Medication Guide is no longer required as part of the REMS but will continue to be part of the approved labeling in accordance with 21 CFR part 208. The sponsor was notified of this on March 29, 2011; their resubmission on June 10, 2011 included a REMS with a communication plan and timetable for submission of assessments only.

2. MATERIALS REVIEWED

The following Arcapta Neohaler (indacaterol maleate) REMS-related materials were reviewed:

- Proposed risk mangement plan submitted with the original NDA 22-383 on December 17, 2008
- Agency's Complete Response Letter dated October 16, 2009
- Division Director Summary Review, Arcapta Neohaler NDA 22383, Badrul A. Chowdhury, M.D., Ph. D., October 16, 2009
- Proposed REMS submissions dated September 28, 2010, April 22, 2011, and June 10, 2011
- FDA comments dated March 14, 2011 and May 27, 2011 (sent June 7, 2011)

3 RESULTS OF REVIEW OF PROPOSED REMS

See the following appendices for the final and approved Arcapta REMS:

- Appendix A: Arcapta REMS document
- Appendix B: Arcapta DHCPL
- Appendix C: Arcapta Dear Medical Society Letter
- Appendix D: Arcapta Printed/Web-based materials

3.1 Goals

The REMS goals for Arcapta Inhalation Powder are:

1. To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes with the long-acting $beta_2$-adrenergic agonists (LABA) including Arcapta Neohaler when used to treat asthma.

2. To inform healthcare providers and prescribers of the appropriate use of Arcapta Neohaler, and its approved indication (COPD).

3.2 REMS Elements

3.2.1 Communication Plan

Novartis Pharmaceuticals Corporation will implement a communication plan to healthcare providers to support the implementation of this REMS. The communication plan will include:

1. A Dear Healthcare Provider Letter (DHCPL)
2. Dear Medical Society Letter
3. Print or web-based materials

The DHCPL will include the new safety information and new prescribing guidelines for LABAs and will be distributed to prescribers of Arcapta Neohaler by direct mail, fax or e-mail communication at least one month prior to first product availability. Novartis Pharmaceuticals Corporation will distribute the REMS communication materials to all pulmonologists, allergists, immunologists, primary care providers, nurse practitioners, and physicians' assistants.

The Dear Medical Society letter (similar in content to the DHCPL) will be distributed to the leadership of the various professional societies on the same timeline as the DHCPL; the Sponsor will ensure that the professional societies disseminate this information to their members.

Novartis Pharmaceuticals Corporation will distribute this letter to the following professional societies: the American College of Allergy, Asthma & Immunology (ACAAI), the American Academy of Asthma, Allergy & Immunology (AAAAI), the American Thoracic Society (ATS), the American College of Chest Physicians (ACCP), the American College of Physicians (ACP), the National Medical Association (NMA), the American Academy of Nurse Practitioners (AANP), the American Academy of Physician Assistants (AAPA), the American Academy of Family Physicians (AAFP) and the COPD foundation.

The printed and web-based information for health care providers will be posted on a Novartis website within 10 days of REMS approval. This information will remain on the website for 3 years. The content of the printed or web-based material will, at a minimum, include the risk information, key risk data from clinical trials, the new prescribing guidelines, current LABAs on the market and approved uses, prescribing information for Arcapta Neohaler, patient counseling information, and questions and answers for healthcare providers.

3.3 REMS Assessment Plan

Novartis Pharmaceuticals Corporation will submit REMS Assessments to FDA annually from the date of REMS approval.

The following information needed for assessments is included in the REMS supporting document:

1. An evaluation of the prescriber understanding of the increased risk of asthma related deaths and the safe use of LABAs.

2. A description of specific measures that would be taken to increase awareness if the assessment of the prescribers indicates that the prescribers' awareness is not adequate.

3. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.

4. An annual assessment and conclusions regarding the success of the REMS in meeting the stated goals.

5. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)

6. An assessment of the communication plan including:

    a. The date of launch of the communication plan (DHCPL, website, and communication to professional societies)
    b. The number of recipients of the DCHP letter
    c. Date(s) of distribution of the DHCP letter
    d. A copy of all documents included in each distribution
    e. The professional societies that you communicated with
    f. Information that the professional societies disseminated to their members and the timing of the dissemination

4 DISCUSSION AND RECOMMENDATIONS:

Novartis Pharmaceuticals Corporation's REMS proposal for Arcapta Neohaler addresses the requirements stipulated by FDA. The proposed REMS for Arcapta Neohaler includes a communication plan with a DHCPL, a Dear Medical Society letter, and printed and web-based educational materials. The DHCP and the Dear Medical Society letters appropriately address the new safety information and the new prescribing guidelines for Arcapta Neohaler. The printed/web-based materials (also reviewed by DPARP for accuracy) provide in-depth information about the use of Arcapta Neohaler including questions and answers for prescribers' education on the subject.

5 CONCLUSION

DRISK finds the proposed REMS for Arcapta to be acceptable and recommends approval of this REMS as submitted on June 10, 2011.

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KENDRA C WORTHY
06/16/2011

CLAUDIA B KARWOSKI
06/16/2011
concur

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

ARCAPTA NEOHALER REMS Interim Comments Set #2

Date:	May 27, 2011
To:	Badrul Chowdhury, M.D., Ph. D., Director Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Through:	Claudia Karwoski, Pharm. D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead:** Yasmin Choudhry, M.D., Medical Officer **DRISK Reviewers:** Kendra Worthy, Pharm. D., Team Leader, DRISK
Subject:	Interim REMS Review Comments Set #2
Drug Name:	Arcapta Neohaler (indacaterol maleate) dry powder for oral inhalation
Indication(s):	For the treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema
Therapeutic Class:	Long-acting $beta_2$-adrenergic agonist (LABA)
Application Type/Number:	NDA 22-383
Applicant:	Novartis
OSE RCM #:	2010-2221

Materials Reviewed

- Arcapta Neohaler (indacaterol maleate inhalation powder), NDA 22-383, amendment to pending application: Response to REMS comments and information request dated March 29, 2011 submitted April 22, 2011

Introduction and Background

This interim review provides comments on the proposed proposed Risk Evaluation and Mitigation Strategy (REMS) for Arcapta (indacaterol) Neohaler submitted by Novartis on April 22, 2011, in response to the FDA comments dated March 14, 2011 (sent March 29, 2011).

FDA comments (Set #1) dated March 14, 2011 addressed:

- Revision of the goals
- Removal of the Medication Guide language from the REMS document/materials
- Revision of the DHCPL to include the new safety information and the new prescribing guidelines
- Providing the actual letter directed to the leadership of the professional societies and the web-based education materials
- Expansion of the proposed list of prescribers and professional societies
- Revision of the timetable of submission of the REMS assessments
- Revision of the information needed for assessments
- Updating the supporting document
- Survey methodology
- General formatting comments

We also recommended the Sponsor refer to the recently approved Brovana and Perforomist REMS when drafting the REMS materials for Arcapta Neohaler.

Comments to DPARP

The Sponsor has, to some extent, made an attempt to be consistent with the Brovana and Perforomist REMs, and accepted most of our comments. We have comments for the Sponsor in the following section; please send these comments to the Sponsor ASAP to facilitate completion of our review.

The Sponsor's proposed REMS differs from the approved COPD REMS as follows:

1. The Sponsor has removed the following prescribing guideline from the REMS document:

   "All LABA, including Arcapta Neohaler, are contraindicated in patients with asthma without use of a long term asthma control."

   The Sponsor provided the following rationale:

"This statement is not included in the currently proposed label, and is therefore proposed for deletion in the proposed REMS. (b) (4) *The proposed REMS will be updated when labeling is finalized."*

We are aware that this particular guideline is under discussion with the Sponsor; please keep in mind that after all negotiations with Sponsor are completed, we will need a clean copy of the REMS document with appended materials from the Sponsor to attach to our review.

2. The boxed warning for Arcapta Neohaler has an additional sentence (b) (4) The Sponsor has not provided a rationale for this. We recommend that this sentence be removed to be consistent with other LABAs.

3. The content of the web-based material is not consistent with the approved LABAs for COPD. See our track changes and comments in Appendix D.

   Note: we have allowed some variations in the past.

   We request that you review the web-based material for adequacy and accuracy of content.

Please let us know if you would like to discuss any of the comments with us prior to sending to the Sponsor.

Following documents are appended to this review:

- REMS document: Appendix A
- DHCPL: Appendix B
- Dear Medical Society letter: Appendix C
- Web-based materials: Appendix D

Comments for the Sponsor

1. Please see our track changes to the REMS document, the DHCPL, the Dear Medical Society Letter, and the Web-based materials.

2. Your proposed goals are acceptable.

3. Addition of the COPD Foundation to the list of professional societies is acceptable.

4. Ensure that the boxed warning and the prescribing guidelines are not only consistent with the Arcapta label but are also consistent with the approved Brovana and Perforomist labels.

5. Make sure that your supporting document is updated to be consistent with the REMS document and the appended materials.

6. Deletion of the following prescribing guideline from the REMS document and the DHCPL is not acceptable:

   "All LABA, inlcuding Arcapta Neohaler, are contraindicated in patients with asthma without use of a long-term asthma control."

   This prescribing guideline must be included to be consistent with the Class labeling change for the LABAs.

7. We note that you omitted the following subsections from the section on Patient Counseling (page 16) in the web-based materials (also see our track changes):

   - Information for Patients
   - Asthma-Related Death
   - Acute Exacerbations or Deteriorations
   - Appropriate Dosing
   - Concomitant Therapy
   - Common Adverse Reactions with Beta2-agonists
   - Instructions for Administration

Provide language for these sections. We refer you to the Brovana and the Perforomist web-based materials.

8. Your REMS language in the REMS document needs to be consistent with the Class LABA REMS language. Delete the following: (b) (4) and replace with: "from approval of the REMS." See track changes.

9. General Comments: Resubmission Requirements and Instructions:

   - Submit the revised proposed REMS for Arcapta Neohaler with attached materials and the REMS Supporting Document. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

16 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

YASMIN A CHOUDHRY
06/08/2011

KENDRA C WORTHY
06/16/2011

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

REMS Interim Comments Set #1

Date:	March 14, 2011
To:	Badrul Chowdhury, M.D., Ph. D., Director Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Through:	Claudia Karwoski, Pharm. D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead:** Yasmin Choudhry, M.D., Medical Officer and Risk Management Analyst **DRISK Reviewers:** Jodi Duckhorn, MA., Social Scientist Kendra Worthy, Pharm. D., Team Leader, DRISK
Subject:	Interim REMS Review Comments Set #1
Drug Name:	Arcapta Neohaler (indacaterol maleate) dry powder for oral inhalation
Indication(s):	For the treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema
Therapeutic Class:	Long-acting beta$_2$-adrenergic agonist (LABA)
Application Type/Number:	NDA 22-383
Applicant:	Novartis
OSE RCM #:	2010-2221

Materials Reviewed

- Arcapta Neohaler (indacaterol maleate), proposed risk mangement plan submitted with the original NDA 22-383 on 12-17-08
- Complete Response Letter dated October 16, 2009
- Division Director Summary Review, Arcapta Neohaler NDA 22-383, Badrul A. Chowdhury, M.d., Ph. D., October 16, 2009
- Arcapta Neohaler (indacaterol maleate), NDA 22-383, proposed Risk Evaluation and Mitigation Strategy (REMS) #0027 submitted 9-28-10

Introduction and Background

This interim review provides comments on the proposed proposed Risk Evaluation and Mitigation Strategy (REMS) for Arcapta (indacaterol) Neohaler submitted by Novartis on September 28, 2010, in response to the FDA Complete Response (CR) letter dated October 16, 2009.

Indacaterol is a new molecular entity that belongs to the class of long-acting $beta_2$-adrenergic agonist (LABA). The proposed indication is COPD, including chronic bronchitis and emphysema. The original application submitted December 17, 2008 included a proposed risk management plan (voluntary) with routine measures.

Efficacy of Arcapta was shown in placebo controlled studies in asthma and COPD patients. The proposed dosing in the original application was 150 mcg and 300 mcg once daily; these dosages were associated with serious adverse events including cardiovascular events, cerebrovascular events, and asthma-related deaths.

The Agency issued a CR letter to Novartis on October 16, 2009, for the following reasons: Unacceptable serious adverse events including cardiovascular, cerebrovascular, and asthma-related deaths at the proposed doses; no clinically meaningful efficacy difference demonstrated between the doses studied; appropriate dosing frequency not explored in clinical studies; and no clinically meaningful advantage demonstrated with 300 mcg dose (over 150 mcg dose), especially in regards to potential safety disadvantages associated with the administration of a higher dose.

The October 16, 2009 CR letter also specified that a REMS will be required in order to ensure that benefits of the drug outweigh the risks. The Sponsor was told that the proposed REMS must include the following:

- A Medication Guide
- A Timetable for Submission of Assessments no less than 18 months, 3 years, and in the 7^{th} year after the REMS approval
- Assessment of the REMS should include an evaluation of patients' understanding of the serious risks of Arcapta Neohaler in the REMS assessment plan.

The Sponsor submitted a Complete Response September 28, 2010, that included dose response evaluation and dose regimen studies. The current proposed dosing is 75 mcg and 150 mcg once daily. An Advisory Committee meeting is scheduled for March 8, 2011. The PDUFA date is April 4, 2011.

The Complete Response also included a proposed REMS with the goals of:

- informing healthcare providers about:
  - the increased risk of asthma-related death in patients taking LABAs
  - the appropriate use of Arcapta Neohaler
- informing patients of other serious risks associated with the use of Arcapta Neohaler

The REMS contained the following elements:

a. A Medication Guide (MG)
b. A communication plan that includes:
   a. A Dear Healthcare Provider Letter (DHCPL)
   b. A letter to the leadership of the professional societies*
   c. Printed or web-based educational materials*
c. A timetable for submission of assessment of the REMS at 18 months, 3 years, and 7 years post-REMS approval.

*These materials are mentioned in the plan for the proposed REMS but were not included in this submission.

Comments to DPARP

Being that Arcapta is a single-ingredient, long-acting beta$_2$-adrenergic agonist indicated for COPD-only, our comments to the Sponsor below are based upon and consistent with our reviews of the Brovana and the Perforomist REMS. See our track chages to:

- REMS document: Appendix A
- DHCPL: Appendix B

The Sponsor needs to submit the actual printed or web-based educational materials and the letter directed to the professional societies, as these materials were not inlcuded in this submission.

As per our discussion this morning regarding MGs and LABAs, we have removed the MG language from the REMS and the DHCPL.

Please let us know if you would like to discuss any of the comments with us prior to sending to the Sponsor.

Comments for the Sponsor

1. Goals:

Revise the goals as follows:

- To inform healthcare providers and prescribers of the increased risk of asthma related death and serious outcomes with the long-acting beta-2-adrenergic agonists (LABAs) including Arcapta Neohaler.

- To inform healthcare providers and prescribers of the appropriate use of long acting beta$_2$-adrenergic agonists (LABAs) including Arcapta Neohaler.

- To inform patients that people with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as indacaterol, the active moiety in Arcapta Neohaler, have been associated with an increased risk of death from asthma related events.

- To inform patients of other serious risks associated with Arcapta Neohaler.

2. Medication Guide (MG)

According to the Draft Guidance for Industry titled Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), the Agency has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS, and may decide the Medication Guide should be required as labeling but not part of a REMS. We have determined that a Medication Guide is not required as part of your proposed REMS; therefore, we have removed the MG language (including patient surveys) from the REMS document/DHCPL. Comments on your proposed Medication Guide will be sent separately.

Make sure that that this change is reflected in your Dear Medical Society letter, printed/web materials and the supporting document.

3. Communication Plan

a. Your plan to distribute the DHCPL within 60 days of REMS approval is acceptable.

b. The DHCPL must include the new safety information and the new prescribing guidelines for LABAs; **this letter must mirror the Brovana and Perforomist DHCPLs.** See the attached DHCPL for our track changes.

c. Submit the letter directed to the leadership of the professional societies for review. In addition to the letter, your communication to the professional societies must include a link to the Arcapta Neohaler website. Your distribution plan for this letter is acceptable.

d. Submit the printed or web-based educational materials for review. These materials will be required to be available on the Arcapta Neohaler website within 30 days of REMS approval and remain on the website for 3 years. **We refer you to the recently**

approved BROVANA and PERFOROMIST REMS communication plan posted on the FDA website to use as an example when drafting these letters/web-based materials. The content of the print or web-based material for must include at a minimum the following:

- Information about the risk
- Key data regarding the risk (e.g. SMART, SNS)
- New prescribing guidelines
- Currently available LABAs and approved uses
- Prescribing information for Arcapta Neohaler
- Patient Counseling Information
- Questions and Answers
- DHCP Letter (for a period of 1 year)

Some optional pieces could include:

- Resource list of future meetings and peer reviewed journal articles related to LABAs
- Links to FDA Alert(s) for the LABAs

e. Expand your proposed list of the professional societies to include the following:

- The American Academy of Allergy, Asthma & Immunology (AAAAI)
- The American College of Allergy, Asthma & Immunology (ACAAI)
- The American Academy of Family Physicians (AAFP)
- The American Academy of Physician Assistants (AAPA)

f. Include nurse practitioners and physician assistants to your list of targeted healthcare providers.

g. Your timetable for submission of assessments at 18 months, 3 years, and 7 years post-REMS approval is unacceptable. You are required to submit the REMS assessments annually from the date of the approval of the REMS.

h. We acknowledge that the October 16, 2009 CR letter specified the REMS assessments at 18 months, 3 years and at 7th year from the REMS approval. The REMS for the class of long-acting $beta_2$-adrenergic agonists (LABAs) requires annual REMS assessments. Therefore, you must submit your revised timetable for submission of assessments no less than annually.

i. Update your REMS supporting document to be consistent with the REMS document and the educational materials.

j. You must include the date of the REMS approval in the REMS document; the date (mm/yyyy) must appear in a header on the top left-hand corner of the first page of the REMS document. For example: Initial REMS Approval: 02/2011

4. Information Needed for Assessment

a. Revise your list of information needed for assessments as follows:

1. An evaluation of the prescriber understanding of the increased risk of asthma related deaths and the safe use of LABAs.
2. A description of specific measures that would be taken to increase awareness if the assessment of the prescribers indicates that the prescribers' awareness is not adequate.
3. A narrative summary with analysis of all reported asthma-related deaths during the reporting period.
4. An annual assessment and conclusions regarding the success of the REMS in meeting the stated goals.
5. Drug use patterns (reasons for use, patient demographics, length of therapy, prescribing medical specialties)
6. An assessment of the communication plan including:
    i. The date of launch of the communication plan (DHCPL, website, and communication to professional societies)
    ii. The number of recipients of the DCHP letter distribution
    iii. Date(s) of distribution of the DHCP letter
    iv. A copy of all documents included in each distribution
    v. The professional societies that you communicated with
    vi. The information that the professional societies disseminated to their members and the timing of the dissemination

b. The following comments are on the proposed methodology for the assessment:

We acknowledge that you provided a brief description of the survey methodology and instruments to assess the REMS. We will defer our comment until the full methodology is submitted, but offer the following guidance as you develop your proposal.

Submit for review the detailed plan you propose to use to evaluate prescribers' understanding about the safe use of Arcapta Neohaler at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." Make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Arcapta Neohaler.

1. Recruit respondents using a multi-modal approach.
   Explain how often you perform non-respondent follow-up or reminders.
   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

   Explain how you select recruitment sites.
   Submit for review any recruitment advertisements.
2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).

3. Define the expected number of prescribers to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
4. Ensure the sample is demographically representative of the population who prescribe the drug, regardless of the condition for which they prescribe it.
5. List the inclusion criteria for prescribers. For example, eligible respondents might be:
    - has prescribed Arcapta Neohaler at least one time in the past 3 months
    - Not currently participating in a clinical trial involving Arcapta Neohaler

   Submit any screener instruments, and describe any quotas of sub-populations (different medical specialties) used.
6. Explain how you administer surveys and the intended frequency.
   Offer respondents multiple options for completing the survey. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person. Explain how you train surveyors.
7. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).
8. Submit for review the introductory text used to inform respondents about the purpose of the survey.
   Tell potential respondents that their answers will not affect their ability to prescribe the drug, and that their answers and personal information will be kept confidential and anonymous.
9. Clarify in your methodology that respondents are eligible for one wave of the survey only.
10. Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
    You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

11. The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating healthcare providers' knowledge of:
    - the serious risks associated with use of Arcapta Neohaler,
    - how to properly prescribe Arcapta Neohaler,
    - how to properly monitor for the serious risks associated with the use of Arcapta Neohaler;

    The assessment does not assess healthcare providers' comprehension of the educational materials.
    Do not offer respondents an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.

13. Ensure the healthcare provider knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials.
    Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure each question has an "I don't know" answer option.
    Randomize the order of the multiple choice responses on each survey.

14. Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions.
    Do not allow respondents the opportunity or ability to go back to previous questions in the survey.
    Explain if and when any education will be offered for incorrect responses.

15. Use the following (or similar) questions to assess receipt and use of the educational materials.

    - Prior to today, which of the following were you aware of or received with regard to Arcapta Neohaler? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	☐	☐
Medication Guide	☐	☐
Dear Healthcare Provider Letter	☐	☐
Something else - please explain:	☐	☐
None of the above	☐	☐

    - Did you read the Full Prescribing Information?
        a) All,
        b) Most,
        c) Some,
        d) None
        e) I did not receive the Arcapta Neohaler Full Prescribing Information

    - Did you read the Medication Guide?
        a) All,
        b) Most,
        c) Some,

d) None
e) I did not receive the Arcapta Neohaler Medication Guide

- Did you read the Dear Healthcare Provider Letter?
  a) All,
  b) Most,
  c) Some,
  d) None
  e) I did not receive the Arcapta Neohaler Dear Healthcare Provider Letter
- Do you have any questions about any of the educational materials related to Arcapta Neohaler? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

C. **General Comments**

Resubmission Requirements and Instructions:

- Submit the revised proposed REMS for Arcapta Neohaler with attached materials and the REMS Supporting Document. Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate WORD documents.

- Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

YASMIN A CHOUDHRY
03/18/2011

KENDRA C WORTHY
03/18/2011

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Pulmonary and Allergy Products (DPAP)

NDA/BLA #s:	NDA 22-383
Products:	Arcapta Neohaler, (indacaterol maleate) inhalation powder hard gelatin capsules, 150/300 mcg
SPONSOR:	Novartis
FROM:	Curtis Rosebraugh, M.D., Director, Office of Drug Evaluation II
DATE:	October 15, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize 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)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology we have determined that a REMS is necessary to ensure the benefits of Arcapta Neohaler (indacaterol maleate) outweigh the risk of asthma related death. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with chronic obstructive pulmonary disease (COPD) is approximately 15.3 million. This estimate is based on using smoking rates on top of the spirometric definition for COPD used in the third National Health and Nutrition Examination Survey (NHANES III).[1]

B. COPD is a chronic progressive lung disease that includes chronic bronchitis, emphysema, or both. The disease is characterized by progressive airflow obstruction. Patients with COPD have progressive shortness of breath, and have frequent exacerbations characterized by increased sputum production and cough, and decline

[1] Stang P, Lydick E, Silberman C, Kempel A, and Keating ET. The Prevalence of COPD. Using Smoking Rates to Estimate Disease Frequency in the General Population. Chest 2000; 117:354S-359S.

in lung function. COPD is the fourth leading cause of death in the U.S.[2] The proposed indication for Arcapta Neohaler (indacaterol maleate) is for maintenance treatment of bronchospasm in COPD patients. Since COPD has significant morbidity, we anticipate that physicians may prescribe Arcapta Neohaler (indacaterol maleate) to their COPD patients.

C. In clinical studies with Arcapta Neohaler (indacaterol maleate), there was improvement in pulmonary function as determined by increases in forced expiratory volume in one second (FEV1). Improvement in pulmonary function was demonstrated in clinical studies in patients with COPD lasting 3 to 12 months in duration.

D. The expected duration of treatment with Arcapta Neohaler (indacaterol maleate) may be indefinite. It is possible that some healthcare providers may maintain some patients with COPD on Arcapta Neohaler (indacaterol maleate) for their lifetime.

E. Arcapta Neohaler (indacaterol maleate) is a long-acting beta-2 agonist (LABA). LABAs are also used for the treatment of asthma, and in this population, LABAs increase the risk of asthma related death. The results of the Salmeterol Multi-Center Asthma Research Trial (SMART) showed that patients receiving a LABA (salmeterol) were at increased risk for fatal asthma events with a relative risk of 4.4 (95% CI: 1.3-15.3) compared to placebo. When Arcapta Neohaler (indacaterol maleate) is approved for patients with COPD, there is concern that patients with asthma could be prescribed Arcapta Neohaler (indacaterol maleate) and should be informed of the risk of asthma-related death. In addition, the following potential serious adverse events are listed in class labeling for LABAs: paradoxical bronchospasm, cardiovascular effects (increase pulse rate, blood pressure, and/or symptoms, ECG changes), hypokalemia, hyperglycemia, and immediate hypersensitivity reactions.

F. Arcapta Neohaler (indacaterol maleate) is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Arcapta Neohaler (indacaterol maleate). 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).

The elements of the REMS will be the Medication Guide and a timetable for submission of assessment of the REMS.

---

[2] Hoyert DL, Arias E, Smith BL, Murphy SL, Kochanek KD. Deaths: Final data for 1999. National Vital Statistics Report 2001; 49: 1-113.

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

/s/

CAROL F HILL
10/16/2009

CURTIS J ROSEBRAUGH
10/16/2009

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 6, 2009
To:	Badrul Chowdhury, M.D. Director **Division of Pulmonary and Allergy Products**
Through:	Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer Jessica M. Diaz, BSN, RN Patient Labeling Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide) and Risk Evaluation and Mitigation Strategy
Drug Name(s):	Arcapta (b) (4) (Indacaterol maleate)
Application Type/Number:	NDA 22-383
Applicant/sponsor:	Novartis Pharmaceuticals
OSE RCM #:	2009-137

The Division of Pulmonary and Allergy Products (DPAP) requested that the Division of Risk Management review proposed patient labeling and Risk Evaluation and Mitigation Strategy (REMS) for New Drug Application (NDA) 22-383 submitted by Novartis Pharmaceuticals Corporation for Arcapta (b) (4) (*proposed*) (indacterol maleate inhalation powder).

DPAP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide and REMS review until such time as the review division plans to address labeling. Please send us a new consult request at that time. This memo serves to close-out the consult request for Arcapta (b) (4) (*proposed*) (indacterol maleate inhalation powder).

Please let us know if you have any questions.

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

/s/

LATONIA M FORD
08/06/2009

JODI M DUCKHORN
08/06/2009