CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022383Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22383 SUPPL # HFD #

Trade Name Arcapta Neohaler

Generic Name indacataerol maleate

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known July 1, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

Reference ID: 2968910

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NA

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

Reference ID: 2968910

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

Reference ID: 2968910

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

Reference ID: 2968910

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Reference ID: 2968910

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 ! !
YES ☐ ! NO ☐
Explain: ! Explain:

Reference ID: 2968910

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Carol Hill, M.S.
Title: Regulatory Health Project Manager, Division of Pullmonary, Allergy, and Rheumatolog Products
Date: July 1, 2011

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Director, Division of Pulmonary, Allergy, and Rheumatology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Reference ID: 2968910

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

BADRUL A CHOWDHURY
07/01/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: Jun. 30, 11

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Revisions VII

Total no. of pages including cover: 20

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 24, 2011, submission and the June 28, 2011 teleconference. We also refer to the June 28, 29, and 30 emails and our teleconference on June 30, 2011. We have included track changes in the attached physician insert. Insertions are underlined and deletions are strike-outs. Submit revised labeling on June 30, 2011.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: CHill/June 30, 2011
Clearance: Barnes/June 30, 2011
Michele/June 30, 2011
Finalized: CHill/June 30, 2011

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
06/30/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 29, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Additional Labeling Comments and Revisions VI

Total no. of pages including cover: 20

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 24, 2011, submission and the June 28, 2011 teleconference. In the attached package insert, we have additional edits to sections 12.2 and 14. To distinguish these revisions, we have highlighted the changes made. We ask that you submit these changes along with your final labeling changes by 12:00 pm on June 30, 2011.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: CHill/June 29, 2011
Clearance: Barnes/June 29, 2011
Michele/June 29, 2011
Finalized: CHill/June 29, 2011

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
06/29/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 29, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Comments and Revisions VI

Total no. of pages including cover: 29

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 24, 2011, submission and the June 28, 2011 teleconference. We have included track changes in the attached physician insert and the medication guide. The insertions are underlined and the deletions are marked-up. Additionally, we request that you update page one of your REMS document to include the following information to be listed below the established name of the drug: class of product per label and the applicant's name and address. Be advised that additional labeling comments and revisions may be forthcoming. Submit revised labeling by 12:00 pm on June 30, 2011.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: CHill/June 29, 2011
Clearance: Barnes/June 29, 2011
Michele/June 29, 2011
Finalized: CHill/June 29, 2011

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
06/29/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 27, 2011

TO: Ann Shea, Director, Drug Regulatory Affairs, Novartis Pharmaceuticals Corporation

FROM: Carol F. Hill, M.S., Senior Regulatory Health Project Manager, Division of Pulmonary, Allergy, and Rheumatology Products

SUBJECT: Applicant's Request for Information

APPLICATION/DRUG: NDA 22383/Arcapta Neohaler

On June 14 2011, Novatis requested that the FDA Pharmacometrics Team provide the code and data used for their presentation at the May 31, 2011 meeting. In response to their request, we provided on June 27, 2011, via email, 3 SAS files which includes the data requested.

Attachment:
Email Correspondence

From: Wang, Yaning
Sent: Wednesday, June 22, 2011 4:03 PM
To: Hill, Carol; Gobburu, Jogarao V
Cc: Michele, Theresa; Lee, Joo-Yeon (CDER)
Subject: RE: Pharmacometrics Request

Attachments: metaArchival.sas; quartileAnalysisArchival.sas; simulationDay15.sas; Readme.pdf

Carol:
Attached is the requested information by the sponsor.
Thanks
Yaning

Yaning Wang, Ph.D.
Associate Director for Science
Division of Pharmacometrics
Office of Clinical Pharmacology
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 301-796-1624
Email: yaning.wang@fda.hhs.gov

"The contents of this message are mine personally and do not necessarily reflect any position of the Government or the Food and Drug Administration."

From: Hill, Carol
Sent: Wednesday, June 15, 2011 7:09 AM
To: Gobburu, Jogarao V; Wang, Yaning
Cc: Michele, Theresa
Subject: FW: Pharmacometrics Request

Good Morning:

Please see the attached email. Novartis has requested the code and data used by Pharmacometrics for the May 31, 2011, presentation.

^j^*Carol*

From: ann.shea@novartis.com [mailto:ann.shea@novartis.com]
Sent: Tuesday, June 14, 2011 5:01 PM
To: Hill, Carol
Subject: Pharmacometrics Request

Hi Carol,

We would like to request the code and data used by the FDA Pharmacometrics group for the analysis presented at the meeting on May 31, 2011, as we would like to understand the FDA's analysis and approach to help us with future projects.

Best regards,

Ann Shea
Novartis Pharmaceuticals Corporation
PH, DRA-RTM
USEH, 405-3071
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA
Phone: +1 862 778-4567
Email : ann.shea@novartis.com

Drafted by: CHill/June 24, 2011
Clearance: Barnes/June 27, 2011
Wang/June 24, 2011
Finalized: CHill/June 27, 2011

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
06/27/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 23, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – Carton/container Labeling Comments and Revisions

Total no. of pages including cover: 3

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010 submissions, and have taken into account your comments in the June 21, 2011, submission regarding carton and container labels.

We have the following labeling comments:

1. We recommend that you put an imprint of the product name or number on the capsule in addition to the logo to address both concerns for safety and linkage to the device. Based on the usability study results, the product name would be the best linkage for correct capsule and device identification; however, we agree that if the font size cannot be large enough to read, the product name on the capsule is of little use to the patient. However, we would like to point out that the imprint on the capsule serves more than linkage purposes. According to 21 CFR 206.10, inclusion of a letter or number in the imprint, while not required, is encouraged as a more effective means of identification than a symbol or logo by itself. In the case of accidental ingestion, an imprint which includes numbers and letters can help rapidly identify the product, which is helpful in determining the proper response.

2. Present the words ‘Arcapta’ and ‘Neohaler’ in the same (b) (4) color. We do not agree that Arcapta and Neohaler should be presented in two different colors. We consider presenting both components of the name in the same color and font as one way to communicate that both 'Arcapta' and 'Neohaler' represent the whole product and therefore should be used together. By presenting Arcapta and Neohaler in two different colors, practitioners and patients may assume that 'Neohaler' is not part of the name and drop the 'Neohaler' component during prescribing of the drug product or consultation about the product. Additionally, presenting the product and device in the same color mimics other currently marketed products with similar configurations, such as Foradil Aerolizer.

Provide revised carton and container labeling by COB on, June 24, 2011. If you have any questions, please call Carol F. Hill, Senior Regulatory Health Project Manager at 301-796-1226.

Drafted: Michele/June 22, 2011

Clearance: Barnes/June 23, 2011

Finalized; CHill/June 23, 2011

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
06/23/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 21, 2011

To: Ann Shea Sr. Assoc. Dir., Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – Labeling Comments and Revisions IV

Total no. of pages including cover: 33

Comments: Please confirm receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010, submissions, and have taken into account your comments in the June 14, 2011, teleconference and June 15, 2011, submission. Track changes from the previous version of the label (PI) faxed, on June 7, 2011 and the Medication Guide faxed, on June 8, 2011 are included. Insertions are underlined and deletions are marked-up. We ask that you respond to all revisions noted in this version of each.

In addition, we have the following labeling comments:

- We have taken into consideration your comments regarding off-label use in asthma and have made revisions to the Boxed Warning and Contraindications. Submit an updated REMS document to reflect these changes.

- Because the meta-analysis for respiratory-related events was conducted post-hoc and there are inherent complexities and assumptions related to its conduct and statistical analysis, it is used primarily for exploratory purposes. As such, we have removed the meta-analysis from the PI.

Provide revised labeling by COB on June 23, 2011. If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

32 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: Michele/June 20, 2011
Clearance: Barnes/June 21, 2011
Finalized: EChung-Davies for CHill/June 21, 2011

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

/s/

EUNICE H CHUNG-DAVIES
06/21/2011
on behalf of Carol Hill

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 16, 2011

To: Ann Shea, Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
E-Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Comments and Revisions III

Total no. of pages including cover: 26

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler (indacaterol)

We are reviewing the label in your October 1 and December 15, 2010, submissions. We are also reviewing the proposed labeling submitted on June 9, 2011, in response to our June 7 and 8 labeling comments. We have the following comments pertaining to the carton and container labeling and dosing device. We have included revisions to the enclosed package insert and medication guide, insertions are underlined and deletions are in strike-out. Please provide revised labeling incorporating the comments and revisions listed below by COB on Monday, June 20, 2011.

Carton and container labeling comments

A. General Comment

1. We note that you are currently conducting a usability study of capsule/device inhalation products to assess effectiveness of the color linkage approach to discourage device interchangeability by COPD patients. Our overall recommendations may be altered based on the results of the study.

B. Capsules

2. Imprint the actual drug name 'Arcapta' on the capsule rather than the proposed bird symbol. The name 'Arcapta' on the capsule will serve two purposes; it will communicate what drug product is contained in the capsule, and it can also remind the patient to use this capsule with the Arcapta Neohaler because the Neohaler device will also have the name Arcapta displayed on front. This may reduce the risk of using this capsule in another device.

C. Blister Labels

3. We recommend utilizing the same color for the blister label as your proposed device and bolding 'Arcapta Neohaler' so that there is better visual differentiation between Arcapta Neohaler blister labels and blister labels from other marketed products.
4. As currently presented the Arcapta Neohaler blister labels are in two different orientations and must be flipped in order to read the labels. Revise the blister labels so that they are presented in the same orientation for increased readability.
5. Include the statement 'Do not swallow capsules' on the blister label and relocate the 'For use with Neohaler only' so that these statements appear where the manufacture statement is located so that it is more prominent and is presented with the product information. These statements should be highlighted but not boxed.

6. Ensure that the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features pursuant to 21 CFR 201.10(g)(2).
7. Remove the NDC number from the sample blister label.

D. Carton Labeling

8. Utilize the same color and font for both 'Arcapta' and 'Neohaler' so that the practitioner and patient understand that Neohaler is appended to Arcapta and is a component of the proprietary name.
9. Revise the 'Dosage' statement to read, 'Usual dosage: See Prescribing Information".
10. Relocate the statement, 'Each capsule contains…', from the principal display panel displays to the back panel in order to have the most important information prominently displayed on the principal panel.

E. Neohaler Dosing Device

11. Ensure that the Arcapta Neohaler has the statement, 'Arcapta Neohaler' and 'For use only with Arcapta capsules' on the device. The name, Arcapta Neohaler should appear on both the cap of the device and the device itself, so that if the cap is lost, the device can still be identified by the product name.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: CHill/June 16, 2011
Clearance History: Barnes/June 16, 2011
Michele/June 15, 2011
Finalized: CHill/June 16, 2011

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
06/16/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 8, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 - REMS II and Labeling Revisions and Comments: Medication Guide

Total no. of pages including cover: 13

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

In our correspondence dated, June 7, 2011, we note that one of the labeling pieces, the medication guide was not attached to the document as stated. Please see the attached medication guide.

If you have any questions, please contact Carol F. Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Enclosure:
Medication Guide

10 Page(s) of Draft Labeling have 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/

CAROL F HILL
06/08/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 7, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 301-862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383- REMS II and Labeling Comments and Revisions

Total no. of pages including cover: 42

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

We are reviewing the label in your October 1 and December 15, 2010, submissions. We are also reviewing the proposed REMS submitted on May 18, 201, in response to our April 25, 2011 REMS comments and revisions. We have the following comments and revisions to the attached package insert, medication guide and REMS. Insertions are underlined and deletions are in strike-out. Only the changes included since our April 25, 2011 correspondence are tracked. Please provide revised labeling incorporating the revisions and comments listed below by COB on Thursday, June 9, 2011.

Comments pertaining to the Package Insert

1. Modify cross reference fonts/styles such that they are consistent throughout the label. Avoid all capital letters if possible.

2. Modify the font and font size consistent throughout the document.

Comments pertaining to the REMS

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.

10. Make boxed warning language consistent with the language for the boxed warning in the attached label.

If you have any questions, please contact Carol Hill, Senior Regulatory Health Project Manager, at 301-796-1226.

Enclosures:
Package Insert
Medication Guide
REMS

38 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: CHill/June 6, 2011
Clearance History: Barnes/June 7, 2011
Michele/June 6, 2011
Finalized: CHill/June 7, 2011

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
06/07/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Clinical Pharmacology Information Request

Total no. of pages including cover: 3

Comments: Please acknowledge receipt and provide your response by COB on May 27, 2011

Document to be mailed: **YES** **xNO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your submission dated, May 18, 2011, to NDA 22383, is currently under review. We have the following comments or request(s) for information:

1. Provide all datasets, programs and outputs for your re-analysis which was stated on page 16 of your recent report: "Novartis comments on the FDA review of the integrated dose response analysis".

2. Use the following instructions when submitting the requested information.

    a. Submit all datasets used for model development and validation as SAS transport files (*.xpt).

    b. Provide a description of each data item in a Define.pdf file.

    c. Submit model codes or control streams and output listings as ASCII text files with the (*.txt) file extension.

Provide your response to this request no later than COB on May 27, 2011. If you have any questions, please contact Carol F. Hill, Regulatory Health Project Manager, at 301-796-1226.

Drafted: CHill/May 23, 2011
Clearance: Lee/May 23, 2011
Wang/May 23, 2011
Gobburu/May 23, 2011
Raggio for Barnes/May 23, 2011
Finalized: CHill/May 23, 2011

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
05/23/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 23, 2011

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol F. Hill, M.S. Senior Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Clinical Information Request

Total no. of pages including cover: 4

Comments: Please acknowledge receipt and submit your response by COB on May 26, 2011.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

Please refer to your September 28, 2010, submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009; our labeling fax dated April 25, 2011; and your response to that fax dated May 18, 2011.

Provide the following information previously requested in the April 25, 2011, labeling fax by, Thursday, May 26, 2011.

The Arcapta Neohaler safety database reflects exposure of (b) (4) patients to Arcapta Neohaler at doses of 75 mcg or greater for at least 12 weeks in six confirmatory clinical trials (See Section 14). In these trials, 449 patients were exposed to the recommended dose of 75 mcg for 3 months, and 144 and 583 COPD patients were exposed to a dose of 150 and 300 mcg for one year, respectively. Overall, patients had a mean prebronchodilator forced expiratory volume in one second (FEV1) percent predicted of XXX. The mean age of patients was 64 years, with (b) (4) of patients aged 65 years or older, and the majority (b) (4) was Caucasian. In these six confirmatory clinical trials, XX% of patients treated with any dose of Arcapta Neohaler reported an adverse reaction compared with XX% of patients treated with placebo. The proportion of patients who discontinued treatment due to adverse reaction was XX% for Arcapta Neohaler-treated patients and XX% for placebo-treated patients. The most common adverse reactions that lead to discontinuation of Arcapta Neohaler were COPD and dyspnea.

The most common serious adverse reactions were COPD exacerbation, pneumonia, angina pectoris, and atrial fibrillation, which occurred at similar rates across treatment groups. **[FDA Comment: Fill in the XXX fields in the highlighted sections to reflect trials B2335S, B2354, B2355, B2336, B2346, and B2334.]**

Table 1 displays adverse drug reactions reported by at least 2% of patients (and higher than placebo) during a 3 month exposure at the recommended 75 mcg once daily dose. Adverse drug reactions are listed according to MedDRA (version 13.0) system organ class and sorted in descending order of frequency.

Table 1 Number and frequency of adverse drug reactions greater than 2% (and higher than placebo) in COPD patients exposed to Arcapta Neohaler 75 mcg for 3 months in multiple dose, controlled trials
[FDA Comment: Provide this information in table format for trials B2354 and B2355.]

Additional adverse drug reactions reported in >1% (and higher than placebo) in patients dosed with 150 or 300 mcg for 12 months were as follows: **[FDA Comment: Provide this information from trials B2334 and B2335S/SE.]**

NDA 22383
Arcapta Neohaler
Novartis Pharmaceuticals Corporation

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

Drafted: Michele/May 23, 2011

Clearance: Raggio for Barnes/May 23/2011

Finalized: CHill/May 23/2011

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
05/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR ETHICS CONSULTATION
Adults and Pediatrics

Sara F. Goldkind, MD, MA
Senior Bioethicist, Office of Good Clinical Practice Program,
10903 New Hampshire Avenue, WO32-5110
Silver Spring, MD 20993-0002
Tel: (301) 796-8342; Fax: (301) 847-8640
Email: sara.goldkind@fda.hhs.gov

FROM: Sally Seymour, Deputy Director for Safety
Center: CDER
Division: DPARP
Requesting Reviewer Name/Email: Sally Seymour, sally.seymour@fda.hhs.gov
RPM/CSO Name/Email: Carol Hill, carol.hill@fda.hhs.gov

DATE	IND/BLA/IDE NO.	NDA//510(K)/PMA NO.
May 9, 2011		22383

PRODUCT NAME:	PRIORITY CONSIDERATION	PRODUCT CLASSIFICATION	DESIRED COMPLETION DATE
Indacaterol	Yes	LABA	May 19, 2011

SPONSOR: Novartis Pharmaceuticals Corporation

PHASE OF PRODUCT DEVELOPMENT

☐ NONCLINICAL ☐ CLINICAL PHASE: ☐ 1 ☐ 2 ☒ 3 ☐ 4 | POPULATION: ☐ PEDIATRICS ☒ ADULTS

REASON FOR REQUEST

☐ NEW PROTOCOL
☐ NEW CORRESPONDENCE
☐ CLINICAL HOLD
☐ RESUBMISSION
☐ SAFETY/EFFICACY(please explain below)

☒ MEETING
☐ PreIND
☐ End of Phase II
☐ Internal
☐ Sponsor
☐ AC Planning

☐ RESPONSE TO DEFICIENCY LETTER
☐ LABELING REVISION
☐ GUIDANCE DEVELOPMENT
☐ INSPECTION REPORT
☐ SUBJECT OF ADVISORY COMMITTEE MEETING
x OTHER (SPECIFY BELOW):

SUPPORTING INFORMATION FOR CONSULT
(please provide electronic copy if possible)

X PROTOCOL
☐ MEDICAL OFFICIER'S REVIEW(S)
x INFORMED CONSENT DOCUMENTS
☐ MEETING PACKAGE

☐ INVESTIGATOR'S BROCHURE
☐ SUPERVISOR'S REVIEW
☐ OTHER CONSULTATIONS
☐ PEER REVIEW ARTICLES

SPECIFIC ETHICAL QUESTION(S) TO BE ADDRESSED

1. Please comment on the assertion that the trials failed to minimize risks to subjects
2. Please comment on the assertion of inadequate informed consents of subjects
3. Please comment on the use of placebo control in patients with chronic obstructive pulmonary disease (COPD)
4. We also welcome any other comments you may have to aid in responding to the letter from Public Citizen.
5.

COMMENTS/SPECIAL INSTRUCTIONS: Indacaterol is a long-acting beta agonist (LABA) under review (NDA 22383) for bronchodilation in patients with COPD. The PDUFA date is July 1, 2011. Public Citizen submitted letters regarding concerns with the clinical program with indacaterol, including the use of placebo control in the clinical trials, failure to minimize risk to participants, and inadequate informed consent (see attached letters).

Request review of informed consent +/- protocols in response to letter submitted by Public Citizen that raised concern regarding trials that were unethical and failed to minimize risks to subjects and satisfy the requirements in DHHS regulations 45 CFR 46.111(a)(1) and 45 CFR46.116(a)(1) and (2). Please see attached protocols with informed consents. DSI is also reviewing the informed consents for compliance with 21 CFR 50.25. Please also comment on the adequacy of the description of the study procedures and risks and benefits and if the informed consent adequately protects research subjects. We appreciate any other comments that you may have to aid in addressing the letter from Public Citizen, especially regarding the use of placebo control in trials in patients with COPD.

Please contact us if you have any questions.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sally Seymour	☒ EMAIL ☐ INTER-OFFICE
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
	Carol Hill

11-2517

Jackson, Valerie

From: O'Grady, Jordana
Sent: Thursday, March 17, 2011 3:46 PM
To: Jackson, Valerie
Subject: FW: Letter Regarding Indacaterol
Attachments: 110316_Follow-up letter to FDA on Indacaterol_FINAL.pdf

---

From: Michael Carome [mailto:mcarome@citizen.org]
Sent: Wednesday, March 16, 2011 10:05 AM
To: Chowdhury, Badrul A; Woodcock, Janet; Commissioner FDA
Subject: Letter Regarding Indacaterol

Dear Drs. Woodcock, Hamburg, and Chowdhury:

Attached please find a letter regarding the drug indacaterol. Original hardcopies will follow by regular mail. Thank you.

Sincerely,

Michael A. Carome, M.D.
Deputy Director, Health Research Group
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Tele: 202-588-7781
Fax: 202-588-7796
email: mcarome@citizen.org
web: www.citizen.org

PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 16, 2011

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Woodcock:

These comments from the Public Citizen Health Research Group are being submitted in follow-up to our testimony presented at the March 8, 2011 meeting of the Food and Drug Administration (FDA) Pulmonary-Allergy Drugs Advisory Committee (PADAC) regarding the drug indacaterol maleate (Arcapta™ Neohaler™).

(1) We urge FDA to (a) reject the March 8 PADAC recommendation to approve indacaterol at a dose of 75 mcg daily, and (b) not approve the New Drug Application for indacaterol – even at the 75 mcg dose – because the lowest dose that provides the desired efficacy at the lowest possible risk in the chronic obstructive pulmonary disease (COPD) population has not been determined.

(2) Further long-term, placebo-controlled, phase 3 studies of indacaterol, in which placebo-control subjects with moderate to severe COPD are randomized to groups that receives substandard (placebo) care for prolonged periods of time, must not be conducted.

FDA Should not Approve Indacaterol, Even at the 75 mcg Dose

Prior FDA Review of Indacaterol

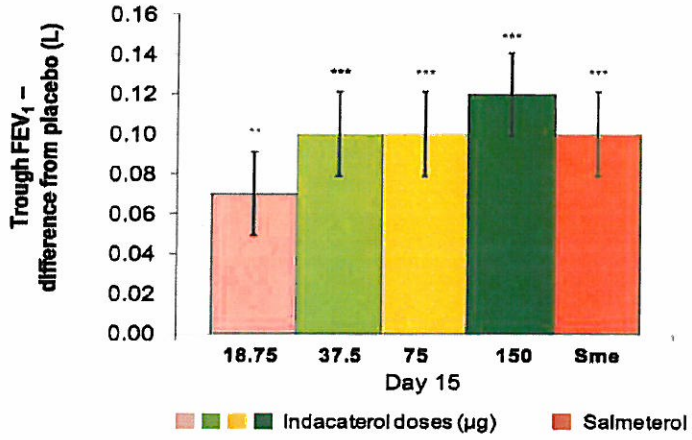
The FDA did not approve Novartis's original application for use of indacaterol at doses of 150 and 300 mcg for COPD because of clinical deficiencies. In particular, the agency concluded that the data submitted did not show meaningful efficacy differences between the proposed doses and a lower dose of 75 mcg, and was concerned about higher frequencies of serious adverse events compared to control subjects in COPD and asthma subjects treated with indacaterol.[1]

The new data submitted by the sponsor and discussed at the March 8 PADAC meeting document the same concerns regarding a possible unfavorable risk:benefit relationship of indacaterol, even at the proposed 75 mcg dose.

Benefit Assessment

For study B2356, a key short-term dose-ranging study in subjects with moderate to severe COPD, the trough FEV1-difference from placebo was identical at the 37.5 and 75 mcg doses (see figure 5-11 below excerpted from Novartis briefing document).[2]

Figure 5-11 Trough FEV_1 (L) at Day 15, B2356, dose-ranging in COPD

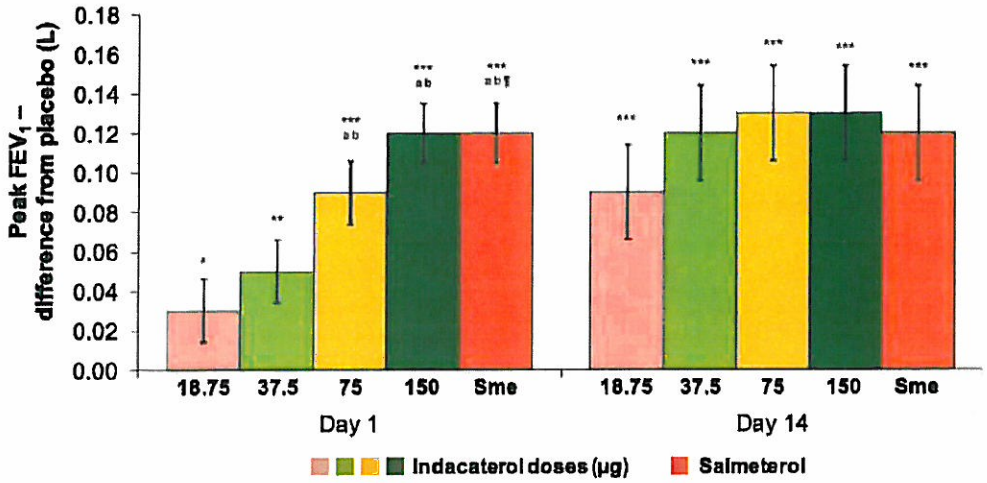


*p<0.05, **p<0.01, ***p<0.001 vs placebo; Data are least squares means ± standard errors (Full analysis set).
Average number of patients per treatment group N=86

Also, peak FEV1-difference from placebo in the first 4 hours post the morning dose on day 14 in study B2356 showed no statistically significant differences between the 37.5 and 75 mcg doses (see figure 5-13 below excerpted from Novartis briefing document).[3]

Reference ID: 2943906

Figure 5-13 Peak FEV_1 (L) in first 4 hours post morning dose, B2356, dose-ranging in COPD



*p<0.05, **p<0.01, ***p<0.001 vs placebo; [a]p<0.05 vs 18.75 µg; [b]p<0.05 vs 37.5 µg; [¶]p<0.05 vs 75 µg; data are least squares means ± standard errors (Full analysis set). Average number of patients per treatment group N=89 (Day 1) and N=86 (Day 14)

The FDA review noted the following regarding the comparison of the 75 and 150 mcg doses of indacaterol:

> On cross study comparison, which has limitations, the bronchodilatory effect sizes do not show a clear efficacy advantage of the 150 mcg dose over the 75 mcg dose.[4]

The FDA statistical reviewer also noted the following regarding data comparing different doses of indacaterol in COPD patients:

> [In] study B2356....The dose of 150 mcg appeared to achieve its maximum bronchodilation effect more rapidly than the other doses, but lost its advantage after two weeks of treatment. Considering indacaterol is proposed to be used as a long term maintenance bronchodilator treatment, the 150 mcg dose's rapid effect in day 1 may not be important, especially balancing with safety concerns on higher dose. **From the week 2 data, it appears indacaterol 37.5 mcg, 75 mcg, and 150 mcg once daily worked equally well in terms of bronchodilatory effect.**[5] [emphasis added]

At this time there is no evidence of any efficacy advantage of the 75 mcg dose over the 37.5 mcg dose, or any dose in between. Thus, the lowest effective dose of indacaterol in patients with moderate to severe COPD has not been established.

Risk Assessment

The phase 3 COPD studies testing indacaterol were not sufficiently powered to detect serious adverse events that may have major adverse public health consequences if the drug is prescribed to millions of COPD patients over many years. Therefore, significant

Reference ID: 2943906

weight must be given to any signal suggesting safety concerns, particularly since indacaterol is not a breakthrough drug and offers no clinically significant advantages over available FDA-approved long-acting bronchodilators.

Such an adverse safety signal has been identified in the FDA's analysis of data from the sponsor's blinded adjudicated analysis comparing indacaterol-treated patients to controls with respect to respiratory-related death, hospitalization, and intubation in all blinded, randomized, controlled trials of 7 or more days of treatment in both asthma and COPD subjects. The FDA medical officer noted the following regarding this data:

> Although the magnitude of the signal is not large, there does appear to be a numerical trend of increasing incidence of acute respiratory-related events, **particularly those that were adjudicated as having been COPD-related,** as the dose of indacaterol rises from 75 mcg to 300 mcg. This increase...is driven primarily by an increase in acute-respiratory related hospitalizations....The possibility that such a signal may exist in COPD rather than asthma **further underscores the importance of selecting the lowest effective dose of a beta-agonist bronchodilator.**[6] [emphasis added]

The dose versus toxicity-response curve for indacaterol is not yet well-defined, but from a public health standpoint, it is reasonable to assume a 37.5 mcg dose will have a lower probability of serious toxicity than a 75 mcg dose.

One supplementary trial submitted to FDA (study B2341) also revealed concerning adverse safety signals. This study, which randomized 1134 subjects with moderate to severe COPD to indacaterol plus tiotropium or placebo plus tiotropium (an ethically designed study), revealed the following:

> The most frequent adverse event was cough, which occurred more frequently in the combination group (10.4% versus 3.7%)...Likewise, discontinuations due to AEs occurred more frequently in the combination group, with 21 (3.7%) versus 9 (1.6%). There were two on-treatment deaths in the trial, both in the combination group. Cause of death was anaphylaxis 30 minutes after receiving ceftriaxone for a COPD exacerbation and myocardial infarction.[7]

This data is consistent with results of a prior meta-analysis by Salpeter et al which showed that inhaled anticholinergics significantly reduced severe exacerbations and respiratory deaths in patients with COPD, whereas β-agonists were associated with increased risk of respiratory deaths.[8]

Concerns about Indacaterol Use in Patients with Asthma

As the FDA is well aware, once approved for the proposed use in COPD patients, indacaterol will be used off-label in asthmatics. Inhaled long-acting β-agonists (LABAs) have been linked to severe asthma exacerbations and asthma-related deaths.[9] In discussing the safety concerns identified in studies of indacaterol in asthmatic patients, the FDA review noted that:

Reference ID: 2943906

> The two deaths in patients with asthma while receiving indacaterol with background of concurrent ICS treatment is concerning. The deaths are reminiscent of asthma-related deaths seen with other LABAs.... The possible imbalance of SAEs related to asthma exacerbation further supports the safety concerns for indacaterol.[10]

Recommendations

In the interests of protecting the public health, the FDA should reject the recommendation of the PADAC to approve indacaterol at the 75 mcg dose and not approve indacaterol at any dose because:

(1) There is no evidence of any efficacy advantage of the 75 mcg dose over the 37.5 mcg dose, or any dose in between. Thus, the lowest effective dose of indacaterol in patients with moderate to severe COPD has not been established

(2) The available data from the studies on indacaterol fail to provide sufficient information to determine whether indacaterol is safe in the intended COPD patient population, even for the 75 mcg dose. The dose versus toxicity-response curve for indacaterol is not yet well-defined, but from a public health standpoint, a 37.5 mcg dose likely will have a lower probability of serious toxicity than the 75 mcg dose.

(3) Indacaterol offers no clinically significant advantages over available FDA-approved long-acting bronchodilators.

(4) Once approved, the drug will certainly be used off-label in asthmatics, who would be placed at increased risk of serious adverse events, including death, from indacaterol, as has been seen with other LABAs.

Further Long-Term, Placebo-Controlled Trials Testing Indacaterol Must not be Permitted

Standard Treatment for Moderate to Severe COPD

Moderate to severe COPD is a serious, life-threatening illness for which regular use of one or more bronchodilators has been the mainstay of treatment. Since at least 2005, the Global Initiative for Chronic Obstructive Lung Disease, a well-recognized authoritative source for COPD management, has had guidelines stating that "regular treatment with one or more long-acting bronchodilators," supplemented with a short-acting β-agonists when needed for acute symptoms and daily inhaled corticosteroids for patients who have frequent exacerbations, should be used to treat moderate to severe COPD.[11]

Reference ID: 2943906

Six Unethical Studies in Which Placebo-Control Subjects Received Prolonged Substandard Care

Despite sponsor and investigator awareness of these standard COPD treatment guidelines,[12,13] Novartis conducted at least 6 pivotal long-term phase 3, placebo-controlled studies (B2335[14], B2334[15], B2346[16], B2336[17], B2354[18], and B2355[19]) in subjects with moderate to very severe COPD, apparently with the endorsement of the FDA.

These studies were unethical primarily because a total of more than 1700 subjects with a serious, life-threatening disease were assigned to placebo groups that received substandard care for prolonged periods of time ranging from 3 to 12 months. In particular, while placebo subjects were permitted to use daily inhaled steroids and short-acting β-agonists for rescue use, they were not permitted to use any LABAs or short- or long-acting inhaled anticholinergics.

Furthermore, based on available data at the time of study initiation, there appeared to be no reasonable state of uncertainty on the part of the investigators regarding the comparative merits of the indacaterol – or the active FDA-approved long-acting bronchodilators used in three of the long term trials – and placebo. As a result, these studies, particularly the most recent ones and the three that used FDA-approved active comparators, lacked equipoise and were therefore unethical.[20]

As the sponsor stated in its briefing document, "[o]ptimizing bronchodilation is **essential** to the management of COPD"[21] [emphasis added]. Not surprisingly, administration of placebo in place of long-acting bronchodilators clearly did not optimize bronchodilation.

Predictably, in all 6 studies, placebo subjects had worse COPD management based on multiple outcome measures than indacaterol subjects or subjects treated with an FDA-approved active comparator. In addition, an analysis of these studies reveals a trend toward an increased death rate in the placebo subjects (0.64%) versus subjects in all active treatment groups combined (0.21%). An analysis by Novartis of subject deaths for the entire COPD safety population and related control subjects showed a similar trend toward an increased death rate in placebo subjects.[22] Among the causes of the 14 placebo-subject deaths noted by Novartis were cardiac arrest, cardio-respiratory arrest, COPD, multiorgan failure, and myocardial infarction. It is highly plausible that substandard care leading to respiratory failure, hypoxemia, and/or respiratory acidosis contributed to the death of some placebo subjects.

The scientific question of whether indacaterol was better than placebo for treating moderate to severe COPD was not an important or clinically useful question, given the existing state of knowledge about COPD treatment at the time these studies were conducted. Rather, the important question is whether indacaterol is at least as good as currently available bronchodilator therapy.

Reference ID: 2943906

Recommendations

Further long-term placebo-controlled trials, involving the withholding of standard bronchodilator therapy, must not be conducted in subjects with moderate to severe COPD. Any ongoing such studies should be terminated immediately.

Thank you for taking our comments into account.

Sincerely,

Michael A. Carome, M.D.
Deputy Director

Sidney M. Wolfe, M.D.
Director
Health Research Group

cc: Dr. Margaret A. Hamburg, Commissioner, FDA
Dr. Badrul A. Chowdhury, Director, Division of Pulmonary, Allergy, and Rheumatology Products, Center for Drug Research and Development, FDA

---

[1] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 3. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[2] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 46. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

[3] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 48. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

[4] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 23. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[5] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 262. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[6] Food and Drug Administration. Addendum to the Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 8. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245638.pdf. Accessed March 4, 2011.

Reference ID: 2943906

[7] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 168.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.
[8] Salpeter SR, Buckley NS, and Salpeter EE. Meta-analysis: anticholinergics, but not β-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med. 2006;21:1011-1019.
[9] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 5.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.
[10] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web page 27.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.
[11] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2005-2010 updates. Available at http://www.goldcopd.com/. Accessed March 4, 2011.
[12] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 112.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.
[13] Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formeterol in COPD. Thorax. 2010;65:473-479.
[14] Donohue JF, Fogarty C, Lötvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182(2):155-62.
[15] Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β_2-agonist indacaterol versus twice-daily formeterol in COPD. Thorax. 2010;65:473-479.
[16] Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med. 2010;10:11.
[17] Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol *versus* twice daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011; 37:273-279.
[18] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 130-141.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.
[19] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 111-129.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.
[20] Freedman B. Equipoise and the ethics of clinical research. NEJM. 1987;317:141-145.
[21] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 14.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.
[22] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 82.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

Reference ID: 2943906

PUBLICCITIZEN

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

March 16, 2011

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

Kristina Borror, Ph.D.
Director, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway
Suite 200
Rockville, MD 20852

Dear Drs. Menikoff and Borror:

We hereby request that the Office for Human Research Protections (OHRP) conduct a compliance oversight evaluation of the following research studies for any U.S. institution that was engaged in the research and held an applicable Federalwide Assurance at the time the research was conducted:

(1) 26 week efficacy, safety and tolerability study of indacaterol in patients with chronic obstructive pulmonary disease (COPD); sponsor: Novartis; ClinicalTrials.gov identifier: NCT00463567; Novartis study number: B2335;[1,2]

(2) Efficacy and safety of indacaterol in patients with COPD; sponsor: Novartis; ClinicalTrials.gov identifier: NCT00624286; Novartis study number: B2346;[3,4]

(3) 12-week efficacy of indacaterol; sponsor: Novartis; ClinicalTrials.gov identifier NCT01072448; Novartis study number: B2354;[5] and

(4) Comparison of efficacy of indacaterol versus placebo over 12 weeks; sponsor; Novartis; ClinicalTrials.gov identifier: NCT01068600; Novartis study number: B2355.[6]

We allege that each of the above-referenced studies, as conducted, was unethical and failed to satisfy the following requirements of the Department of Health and Human Services regulations at 45 CFR part 46:

(1) 45 CFR 46.111(a)(1): The research as conducted failed to minimize risks to subjects because study design was unsound and unnecessarily exposed subjects to risk. In particular, in each study large numbers of placebo-control subjects with moderate to severe COPD were randomized to a study group that received substandard (placebo) care for up to 3 to 6 months.

(2) 45 CFR 46.116(a)(1) and (2): It is likely that the IRB-approved informed consent process and document failed to adequately describe the procedures involved in the research and reasonably foreseeable risks and discomforts to the subjects with respect to the placebo-control group subjects.

The following discussion provides a detailed overview of the rationale for our allegations.

Failure to Minimize Risks to Subjects

Standard Treatment for Moderate to Severe COPD

Moderate to severe COPD is a serious, life-threatening illness for which regular treatment with one or more long-acting bronchodilators, such as long-acting β-adrenergic agonists (LABAs)(e.g., salmeterol and formoterol) or long-acting anticholinergic agents (e.g., tiotropium), has been the mainstay of treatment for many years. Since at least 2005, the Global Initiative for Chronic Obstructive Lung Disease, a well-recognized authoritative source for COPD management, has had guidelines stating that "regular treatment with one or more long-acting bronchodilators," supplemented with a short-acting β-agonists when needed for acute symptoms and daily inhaled corticosteroids for patients who have frequent exacerbations, should be used to treat moderate to severe COPD.[7]

Six Unethical Studies in Which Placebo-Control Subjects Received Prolonged Substandard Care

Despite sponsor and investigator awareness of these standard COPD treatment guidelines and the importance of optimizing bronchodilation in moderate to severe COPD[8,9], the 6 pivotal, long-term, phase 3, placebo-controlled studies listed in the Table below were conducted in subjects with moderate to very severe COPD, apparently with the endorsement of the FDA (studies B2334 and B2336 were conducted entirely outside the U.S.).

These studies were unethical primarily because a total of more than 1700 subjects with a serious, life-threatening disease were assigned to placebo groups that received substandard care for prolonged periods of time ranging from 3 to 12 months. In particular, while placebo subjects were permitted to use daily inhaled steroids (if already on such steroids at a stable dose at the time of study enrollment) and short-acting β-agonists for rescue use, they were not permitted to use any LABAs or short- or long-acting inhaled anticholinergics or to start inhaled corticosteroids.

Reference ID: 2943906

Furthermore, based on available data at the time of study initiation, there appeared to be no reasonable state of uncertainty on the part of the investigators regarding the comparative merits of the indacaterol – or the active FDA-approved long-acting bronchodilators used in three of the long term trials – and placebo. As a result, these studies, particularly the most recent ones and the three that used FDA-approved active comparators, lacked equipoise and were therefore unethical.[10]

As the sponsor stated in a briefing document recently submitted to the FDA, "[o]ptimizing bronchodilation is **essential** to the management of COPD" [11] [emphasis added]. Not surprisingly, administration of placebo in place of long-acting bronchodilators clearly did not optimize bronchodilation.

TABLE: Description of Long-Term Randomized, Placebo-Controlled Studies Testing Indacaterol

Study #	Dates of Enrollment	Active Treatment Intervention	# of Placebo Subjects	Duration
B2335[12]	April 07-August 08	Indacaterol 150 mcg (N=416) Indacaterol 300 mcg (N=416) Tiotropium 18 mcg (N=415)	418	6 months
B2334[13]	?-2008	Indacaterol 300 mcg (N=437) Indacaterol 600 mcg (N=425) Formoterol 12 mcg bid (N=434)	432	12 months
B2346[14]	?-2008	Indacaterol 150 mcg (N=211)	205	3 months
B2336[15]	Nov 2007-Jan 2009	Indacaterol 150 mcg (N=330) Salmeterol 50 mcg (N=333)	335	6 months
B2354[16]	?-2010	Indacaterol 75 mcg (N=163	160	3 months
B2355[17]	?-2010	Indacaterol 75 mcg (N-159)	159	3 months

Predictably, in all 6 studies, placebo subjects had worse COPD management based on multiple outcome measures than indacaterol subjects or subjects treated with an FDA-approved active comparator. In addition, an analysis of these studies reveals a trend toward an increased death rate in the placebo subjects (0.64%) versus subjects in all active treatment groups combined (0.21%). An analysis by Novartis of subject deaths for the entire COPD safety population and related control subjects showed a similar trend toward an increased death rate in placebo subjects.[18] Among the causes of the 14 placebo-subject deaths noted by Novartis were cardiac arrest, cardio-respiratory arrest, COPD, multiorgan failure, and myocardial infarction. It is highly plausible that substandard care leading to respiratory failure, hypoxemia, and/or respiratory acidosis contributed to the death of some placebo subjects.

The scientific question of whether indacaterol was better than placebo for treating moderate to severe COPD was not an important or clinically useful question, given the existing state of knowledge about COPD treatment at the time these studies were conducted. Rather, the important question is whether indacaterol is at least as good as currently available bronchodilator therapy.

Reference ID: 2943906

Inadequate Informed Consent of Subjects

While adequate informed consent would not have been sufficient to make these studies ethical, it is likely that subjects were not informed that they had a 25 to 50% chance of being assigned a substandard treatment regimen for 3 or 6, and that they were almost certainly likely to experience more shortness of breath, more dyspnea on exertion, decreased exercise tolerance, more frequent COPD exacerbations, and an increased risk of death since they would not be receiving the usual standard medical care with regular use of long-acting bronchodilators.

FDA Involvement

It is our understanding that OHRP routinely refers complaints about industry-sponsored clinical trials to FDA for review and action. In this case, it is clear that FDA has a conflict of interest and should not be asked to investigate our allegations because Novartis conducted these placebo-controlled trials with the full knowledge and endorsement of the FDA. Therefore, since FDA is complicit in this unethical research, we urge OHRP to take the lead in investigating our allegations. We acknowledge that OHRP may need FDA's assistance in identifying the U.S. institutions that were engaged in each of the above-referenced studies since, except for study B2335, the citations on ClinicalTrials.gov do not provide the specific names of the research institutions enrolling subjects for each study.

Please note that OHRP may share our complaint letter with identifiers with anyone. We will be posting a copy on our website as well.

We look forward to OHRP's thorough and careful investigation of our allegations. Please contact us if you have any questions or need additional information.

Sincerely,

Michael A. Carome, M.D.
Deputy Director

Sidney M. Wolfe, M.D.
Director
Health Research Group

Reference ID: 2943906

Enclosures:
(1) ClinicalTrial.gov citations for studies NCT00463567, NCT00624286, NCT01072448, and NCT01068600.
(2) Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182:155-162.
(3) Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomized, 12-week study. BMC Pulm Med. 2010;10:11.

cc: Honorable Kathleen Sebelius, Secretary of Health and Human Services

---

[1] ClinicalTrials.gov citation for NCT00463567. http://clinicaltrials.gov/ct2/show/study/NCT00463567?term=b2335&rank=2&show_locs=Y#locn. Accessed March 14, 2011.
[2] Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182:155-162.
[3] ClinicalTrials.gov citation for NCT00463567. http://clinicaltrials.gov/ct2/show/study/NCT00463567?term=b2335&rank=2&show_locs=Y#locn. Accessed March 14, 2011.
[4] Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomized, 12-week study. BMC Pulm Med. 2010;10:11.
[5] ClinicalTrials.gov citation for NCT01072448. http://clinicaltrials.gov/ct2/show/study/NCT01072448?term=b2354&rank=1&show_locs=Y#locn. Accessed March 14, 2011.
[6] ClinicalTrials.gov citation for NCT01068600. http://clinicaltrials.gov/ct2/show/study/NCT01068600?term=b2355&rank=1&show_locs=Y#locn. Accessed March 14, 2011.
[7] Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; 2005-2010 updates. Available at http://www.goldcopd.com/. Accessed March 4, 2011.
[8] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 112. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.
[9] Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β2-agonist indacaterol versus twice-daily formeterol in COPD. Thorax. 2010;65:473-479.
[10] Freedman B. Equipoise and the ethics of clinical research. NEJM. 1987;317:141-145.
[11] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 14. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.
[12] Donohue JF, Fogarty C, Lötvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med. 2010;182(2):155-62.
[13] Dahl R, Chung KF, Buhl R, et al. Efficacy of a new once-daily long-acting inhaled β_2-agonist indacaterol versus twice-daily formeterol in COPD. Thorax. 2010;65:473-479.
[14] Feldman G, Siler T, Prasad N, et al. Efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med. 2010;10:11.
[15] Kornmann O, Dahl R, Centanni S, et al. Once-daily indacaterol *versus* twice daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011; 37:273-279.
[16] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 130-141. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

Reference ID: 2943906

[17] Food and Drug Administration. Pulmonary-allergy drugs advisory committee briefing materials for March 8, 2011. Web pages 111-129. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf. Accessed March 4, 2011.

[18] Novartis. Indacaterol (QAB149) in Chronic Obstructive Pulmonary Disease (NDA 22-383) Briefing Document. February 1, 2011. Web page 82. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245639.pdf. Accessed March 4, 2011.

1541 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 2943906

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
05/09/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 25, 2011

To: Ann Shea Sr. Assoc. Dir., Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy and Rheumatology Drug Products
Email Address: ann.shea@novartis.com	**Fax number:** 301-796-9728
Phone number: 301-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Labeling Comments and Revisions II

Total no. of pages including cover: 25

Comments: Please acknowledge receipt.

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

We are reviewing the label in your October 1 and December 15, 2010 submissions. Additional labeling comments will be forthcoming as we continue to review the labeling. Insertions are underlined and deletions are marked-up. Please note that sections 6 and 14 have been completely rewritten, so track changes are not included. We ask that you respond to all revision noted in this version.

If you have any questions, please contact Carol Hill, Senior Regulatory Project Manager, at 301-796-1226.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: CHill/April 25, 2011
Clearance: Barnes/April 25, 2011
Buenconsejo/April 18, 2011
Michele/April 18, 2011
Seymour/April 19, 2011
Chowdhury/April 19 & 22, 2011
Finalized: CHill/April 25, 2011

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
04/25/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: March 29, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager carol.hill@fda.hhs.gov
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – REMS Comments and Information Request

Total no. of pages including cover: 16

Comments: Please acknowledge receipt.

Document to be mailed: YES ☑NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Your resubmitted NDA dated, October 1, 2010, for Arcapta Neohaler is currently under review. The enclosed Risk Evaluation and Mitigation Strategy (REMS) document contains clarification comments for some of the changes made to the proposed REMS. The FDA-proposed insertions are underlined and deletions are in strike-out. These comments are not all inclusive and we may have additional comments as we continue our review. Submit a revised REMS to include the recommendations listed below and incorporate the changes shown in the attached marked up REMS.

If you have any questions, please contact Carol Hill, Regulatory Project Health Manager, at 301-796-1226.

Enclosure: Recommendations to the REMS

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.

Reference ID: 2925260

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; (b) (4)

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. 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.

Reference ID: 2925260

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

i. 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, in addition to the presentation 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.

Reference ID: 2925260

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

Reference ID: 2925260

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
03/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383

REVIEW EXTENSION – MAJOR AMENDMENT

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey

Attention: Ann Shea
Director, Regulatory Affairs

Dear Ms Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler (indacaterol maleate inhalation powder), 150/300 mcg per capsule.

On February 8, 2011, we received your solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 1, 2011.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 14, 2011.

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

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief Project Management Staff
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

CAROL F HILL
03/22/2011
Signed for Sandy Barnes

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 24, 2011

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corporation	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22-383 – Clinical Information Request

Total no. of pages including cover: 3

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals, Corporation
Arcapta Neohaler

Your submission dated February 8, 2011, to NDA 22-383 is currently under review. We have the following requests for information:

The following table provides incidences of total respiratory- and acute-respiratory related events as a composite, and is divided by hospitalizations and intubations in the All-treated COPD Safety Population I.

Total and Acute Respiratory-Related Events: All-treated COPD Population I										
	Indacaterol Treatment Groups (mcg)						**Active Comparators**			
	75 n=543	**150 n=2745**	**150 +Tio n=1142**	**300 n=1422**	**600 n=584**	**ALL n=6863**	**For n=556**	**Tio n=842**	**Sal n=1010**	**PBO n=2484**
Composite n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	54 (3.8)	15 (2.6)	134 (2.0)	32 (5.8)	7 (0.8)	14 (1.4)	52 (2.1)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	47 (3.3)	15 (2.6)	120 (1.8)	31 (5.6)	6 (0.7)	12 (1.2)	50 (2.0)
Hospitalizations n(%)										
Total	6 (1.1)	43 (1.6)	16 (1.4)	53 (3.7)	15 (2.6)	133 (1.9)	32 (5.8)	7 (0.8)	14 (1.4)	50 (2.0)
Acute	6 (1.1)	37 (1.3)	15 (1.3)	46 (3.2)	15 (2.6)	119 (1.7)	31 (5.6)	6 (0.7)	12 (1.2)	47 (1.9)
Intubations n(%)										
Total	0	1	1	2 (0.1)	0	4 (0.1)	3 (0.5)	0	1	1
Acute	0	1	0	1 (0.1)	0	2	3 (0.5)	0	0	1

1. Provide exposure-adjusted incidences for each of the values listed in the table.

2. Similarly, provide exposure-adjusted incidences for the All-treated and All-treated Asthma Safety Populations as well.

We request your reply by COB, Monday, February 28, 2011. If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: Karimi-Shah/February 23, 2011
Clearance History: Michele/February 23, 2011
Barnes/February 24, 2011
Finalized: chill/February 24 2011

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
02/24/2011

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Pulmonary and Allergy Products

Memorandum of Facsimile Correspondence

Date: February 18, 2011
To: Ann Shea, Senior Associate Director, Drug Regulatory Affairs
Company: Novartis Pharmaceutical Corporation
Email Address: ann.shea@novartis.com
Phone: 867-778-4567
From: Carol Hill, MS
Regulatory Health Project Manager
Division of Pulmonary, Allergy and Rheumatology Products

Subject: NDA 22383 – Labeling Comments and Revisions I
# of Pages: 24

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.
carol.hill@fda.hhs.gov

NDA 22383
Novartis Pharmaceutical Corporation
Arcapta Neohaler

We have begun our review of the label in your October 1 and December 15, 2010 submissions. Be advised that additional labeling comments will be forthcoming as we continue to review the labeling. Also be advised that the comments provided are not final and no decision on approvability, dose, dose regimen, indication or other claims has been made.

Note that we have not provided comments on the following sections: Highlights, Section 6 (Adverse events), Section 14 (Clinical Trials), and Section 17.5 (Medication Guide). Since we will be providing our revisions and comments to specific sections of the labeling, we do not expect you to provide revised labeling at present. However, if you have questions regarding any of the revised sections, we request that you forward your comments so that we may address any issues you may have. In the attached revised package insert labeling, insertions are underlined and deletions are strike-out.

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

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Drafted by: Chill/February 17, 2011
Clearance: Barnes/February 17, 2011
Fan/February 17, 2011
Xu/February 17, 2011
Michele/February 17, 2011
Finalized: Chill/February 18, 2011

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
02/18/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 16, 2011

To: Ann Shea Senior Associate Director, Drug Regulatory Affairs	**From: Carol Hill, M. S.** **Regulatory Health Project Manager**
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-8565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22-383 (indacaterol) – Clinical Information Request

Total no. of pages including cover: 2

Comments: Please acknowledge receipt.

Document to be mailed: **YES** **xNO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your submission dated February 8, 2011, to NDA 22-383 is currently under review. We have the following comments or request(s) for information:

1. Provide a listing of deaths from the safety database that were not included in this analysis and the reason for exclusion.

2. Provide the narratives and adjudication listing for all events included in the analysis.

3. In reference to Table 7-2: Provide an explanation as to why the number of non-respiratory events together with the respiratory events is lower than the total number of patients with adjudicated narratives.

4. In reference to Table 7-2: Provide a further breakdown of the numbers of deaths, hospitalizations, and intubations under the subdivisions of asthma-, COPD-, and pneumonia-related.

5. It appears that the events in the IND OTH (other device) category are not included in the IND ALL category. Provide the indacaterol dose group for those events which occurred in the IND OTH category.

We request your reply by COB, Thursday, February 17, 2011. If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: Karimi-Shah/February 15, 2011
Clearance History: Michele/February 15, 2011
Barnes/February 16, 2011
Finalized: chill/February 16, 2011

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
02/16/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022383

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) dated October 1, 2010, received October 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indacaterol Maleate Inhalation Powder, 75 mcg and 150 mcg.

We also refer to your November 19, 2010, correspondence, received November 19, 2010, requesting review of your proposed proprietary name, Arcapta Neohaler. We have completed our review of the proposed proprietary name, Arcapta Neohaler and have concluded that it is acceptable. The proposed proprietary name will be re-reviewed 90 days before approval of the NDA. If we find the name unacceptable following re-review, we will notify you.

We also refer to your November 19, 2010 request to receive confirmation that the proposed proprietary name Arcapta Neohaler would also be acceptable if the product were to have only a single strength of either 75 mcg or 150 mcg. At this time our assessment of the proposed proprietary name Arcapta Neohaler can only consider the proposed product characteristics as listed in the November 19, 2010 submission, therefore if **any** of the proposed product characteristics as stated in this submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Carol Hill, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
02/15/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 12, 2011

To: **Ann Shea** **Director, Drug Regulatory Affairs**	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 –Statistical Response to Submission dated, December 24, 2010

Total no. of pages including cover: 3

Comments: Please acknowledge Receipt

Document to be mailed: **YES** **xNO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Your submission dated December 24, 2010, in response to our December 16, 2010 Clinical Information Request, is currently under review. We have the following comments or requests for information regarding the statistical analysis plan.

1. In Section 2.1, add the following analysis sets: a) placebo-controlled COPD studies and b) placebo-controlled asthma studies.

2. In Section 2.6.2.1, clarify what is meant by "If a patient experiences multiple events only first event of a particular type will be considered." Does this mean that for each type of event listed in Section 2.6.2.2, a separate analysis will be conducted and multiple events refer only to the event being analyzed?

3. In Section 2.6.2.2, perform additional Cox models regressions stratified only by study.

4. In Section 3.1, use 4 decimal places in reporting events per year.

If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: CHill/January 11, 2011
Clearance History: Barnes/January 11, 2011
Levenson/January 11, 2011
Liu/January 11, 2011
Buenconsejo/January 11, 2011
Michele/January 11, 2011
Seymour/January 11, 2011
Finalized: CHill/January 12, 2011

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
01/12/2011

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 28, 2010

To: **Ann Shea** **Director, Drug Regulatory Affairs**	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp	Division of Pulmonary, Allergy, Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 – Clinical Response to Submission dated, December 24, 2010

Total no. of pages including cover: 3

Comments: Please acknowledge Receipt

Document to be mailed: **YES** **xNO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Your submission dated December 24, 2010, in response to our December 16, 2010 Clinical Information Request, is currently under review. We have the following comments or requests for information. Please note that additional comments regarding the statistical analysis plan will be provided soon.

1. As soon as possible, submit a table of the studies with indacaterol that you plan to exclude in the analysis and the reason that each study is excluded.

2. For cause of death, all non-respiratory related events will be listed as "non-respiratory". Specific cause of death should be determined by the committee even if non-respiratory. Categories such as MI, sudden death, stroke, etc. are encouraged rather than preferred terms. Include a comparison with the preferred term cause of death as determined by the investigator.

3. The Adjudication Committee Charter notes that AC members may ask for additional information only in the event of a disagreement between members, [Step 4, p.15]. There should be some mechanism by which members may ask for additional information earlier in the process.

4. Include subgroup analysis for trials of 7 days treatment duration and less vs. trials longer than 7 days treatment duration for both asthma and COPD.

If you have any questions, please contact Carol Hill, Regulatory Project Manager, at 301-796-1226.

Drafted by: Seymour/12-27-10
Clearance History: Chowdhury/12-27-10
Barnes/12-28-10
Finalized: CHill/12-28-10

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
12/28/2010

Food and Drug Administration
Center for Drug Evaluation and Research
OFFICE OF DRUG EVALUATION II

FACSIMILE TRANSMITTAL SHEET

DATE: December 20, 2010

To: Ann Shea Director, Regulatory Affairs	**From:** Carol Hill, MS Regulatory Health Project Manager
Company: Novartis Pharmaceutical Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Email address: **ann.shea@novartis.com**	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: NDA 22383 – Statistical Information Request

Total no. of pages including cover: **5**

Comments: Please acknowledge your receipt.

Document to be mailed: YES XNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

Your submission dated, September 28, 2010, received, October 1, 2010 for NDA 22383 is currently under review. We have the following comments or request for information.

1. In your submitted dataset “qab149b2336\analysis\aspider.xpt”, the SGRQ score imputed with LOCF (param_1a=”TOT_L”) is identical to the unimputed SGRQ score (param_1a=”TOT”). Please explain why the two sets of scores are identical. Submit your dataset with unimputed SGRQ (the total score and three components) by visit, including a column that flags whether the patient discontinued or not, a column with reasons for discontinuation, a column indicating at which visit the patient discontinued. Add visit 999 with imputed SGRQ scores by LOCF. The dataset should also include all the variables that are included in the ANCOVA model. We have the same request for studies B2335s, B2334, B2346, B2354 and B2355.

2. On page 108 of your clinical study report of CQAB149B2336, you reported the ANCOVA result on SGRQ total score in table 11-7. The snapshot of the table is shown below for your reference. In dataset “qab149b2336\analysis\aspider.xpt”, the number of subjects with imputed SGRQ total score at week 12 (param_1a=”TOT_L” & visnam1a=”Day 84”) are 302 for Indacaterol 150 mcg, 293 for Salmeterol, and 274 for placebo. Please explain the discrepancy between the dataset and your result. We found similar discrepancy for studies B2334, B2346, B2335s, B2354 and B2355. Provide explanation for those studies as well.

Table 11-7 SGRQ total score at Week 12: treatment comparisons (ITT population)

		Treatment			Treatment difference			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95% CI	p-value
Ind 150 µg	309	36.4	1.04	Ind 150 µg - Pbo	-6.3	0.99	(-8.2,-4.3)	<.001*
				Ind 150 µg - Salm	-2.1	0.99	(-4.0,-0.2)	0.033
Salm	301	38.5	1.04	Salm - Pbo	-4.2	1.01	(-6.1,-2.2)	<.001
Pbo	294	42.6	1.05					

3. Fill out the following two table shells based on both imputed and unimputed SGRQ scores. Provide similar summaries for studies B2334, B2346, B2335s, B2354 and B2355, i.e. the same table header with proper treatment arms in each study.

Study ID	SGRQ Score	Treatment	Number of subjects in ITT	Number of patients with non missing data	Baseline (arithmetic mean)	Week 12 (arithmetic mean)	Changing from baseline at week 12 (arithmetic mean)
B2336	Total	Ind 150 mcg					
		Salmeterol					
		Placebo					
	Activity	Ind 150 mcg					
		Salmeterol					
		Placebo					
	Impact	Ind 150 mcg					
		Salmeterol					
		Placebo					
	Symptom	Ind 150 mcg					
		Salmeterol					
		Placebo					

Study ID	SGRQ Score	Treatment	Number of subjects in ITT	Number of patients with non missing data	Number of subjects included in ANCOVA	LS mean of treatment effect at week 12	SE	Comparison	LS mean	SE	95% CI	P
B2336	Total	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				
	Activity	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				
	Impact	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				
	Symptom	Ind 150 mcg						Ind 150 mcg – pbo				
		Salmeterol						Salm – pbo				
		Placebo						Ind 150 mcg – Salm				

Please respond to our request by COB on December 27, 2010 with a formal submission to the application. If you have any questions, call Carol Hill, Regulatory Health Project Manager at 301-796-1226.

Drafted by: liu/12-20-10
Clearance: Barnes/12-20-10
Buenconsejo/12-20-10
Finalized: chill/12-20-10

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
12/20/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383 **INFORMATION REQUEST**

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We also refer to your September 28, 2010 submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009.

In our action letter for your original submission, we stated the following:

> *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.*

In addition to the risk benefit assessment of indacaterol in COPD patients, another important potential safety issue noted in the action letter is possible asthma-related death. Additional information is required to address these issues. To facilitate our safety review of your product, we have the following request for information.

Conduct an analysis evaluating the incidence of respiratory-related death, intubation, and hospitalization in indacaterol-treated patients compared to control. Use the following criteria to provide guidance in formulating your analysis.

1. <u>Study inclusion criteria</u>
   a. Include all blinded, parallel-arm, randomized, controlled trials of 7 or more days treatment duration that were conducted with indacaterol maleate delivered using the single dose dry powder inhaler Concept 1 device (to-be-marketed indacaterol product) for the treatment of COPD or asthma, whether or not the trials were submitted as part of the NDA.

b. Include trials in which the to-be-marketed indacaterol product was administered as randomized treatment, either with or without a concomitant inhaled corticosteroid (ICS) or other adjunctive therapy. Include trials conducted with indacaterol combination products that have a treatment arm(s) using the to-be-marketed indacaterol product.

c. Include trials with any dose of the to-be-marketed indacaterol product.

d. Include both placebo- and active-controlled trials.

e. Include trials in which there was a randomized blinded phase followed by an open label extension phase. However, include only the blinded phase of the trial in your analysis.

f. Include randomized, double-blind crossover design trials. However, include only the first cross-over period of the trial.

g. Do not include trials in healthy volunteers, indications other than asthma or COPD, uncontrolled trials, or trials designed primarily to obtain clinical pharmacology data (e.g., Phase I trials).

h. Do not include trials in children less than 12 years of age.

i. Do not include trials conducted solely with devices other than the Concept 1 device or with other formulations of indacaterol, such as alternative salts.

2. <u>Identification and adjudication of events</u>
   a. Adverse events of interest to include:

      1. all-cause death,

      2. asthma-related death,

      3. asthma-related intubation,

      4. asthma-related hospitalization,

      5. COPD-related death,

      6. COPD-related intubation,

      7. COPD-related hospitalization,

      8. pneumonia-related death,

      9. pneumonia-related intubation, and

10. pneumonia-related hospitalization.

b. Review all serious adverse events reported in the trials, in a manner blind to treatment, to determine whether the event involved death, hospitalization, or intubation. For events involving one or more of these outcomes, determine whether the event occurred in the setting of an acute respiratory event or was otherwise respiratory-related. Base the determination of respiratory-relatedness on the clinical judgment of an independent adjudication committee. Do not rely upon the coded adverse event term to determine respiratory-relatedness, as the reliability and validity of the specific terms may be variable.

c. For the analysis of individual events, a patient may have more than one respiratory event related to a single experience. For example, a patient who had an asthma-related hospitalization, followed by an asthma-related intubation and died of an asthma-related cause should be considered as having each of four events. All four events are to be counted in the analysis, not just the most critical.

d. Count on-treatment events, not events that occurred after treatment. Include events regardless of determination of drug-relationship.

e. For each patient who died during the trial, provide cause of death as determined by an independent adjudication committee. Compare the adjudicated cause to the adverse event resulting in death as determined by the investigator.

f. Provide narrative summaries for each patient with an adverse event of interest.

3. <u>Statistical methods</u>

a. Analyze event rates based on exposure. Include time to event analyses and hazard ratios compared to placebo. Consider methods with statistical properties suited for the known incidence rates.

b. Consider composite endpoints of all COPD-related events, all asthma-related events, and all respiratory-related events. For composite endpoints, count only the first event if more than one event occurred for a single patient.

c. Include all available blinded, controlled data for a trial. Do not truncate based on an arbitrary cut off date.

d. Include at least the following analysis sets:

1. all included studies conducted using the to-be-marketed product,

2. placebo-controlled studies,

3. COPD only studies,

4. asthma only studies, and

5. COPD only studies greater than 7 days duration.

b. Complete the analyses for each individual indicaterol dose. Also do an analysis with all indacaterol dosage groups combined.

c. For COPD only studies, conduct a subgroup analysis of patients with baseline bronchodilator responsiveness compared to non-bronchodilator responsive patients. Define bronchodilator responsiveness according to the American Thoracic Society criteria of FEV1 change of >200 ml and >12%. [Pellegrino R, Viegi G, Brusasco RO, et al. Interpretive strategies for lung function testing. *Eur Respir J* 2005; 26:948-68.]

d. Summarize non-completers by treatment group. Include reasons for non-completion, follow-up time after dropout, AEs of interest before dropout, and any known AEs of interest after dropout.

Please provide your proposed analysis plan and timeline for analysis completion by COB on January 2. Also provide in your timeline the planned date of submission of your Adjudication Committee charter. Include a detailed description of the procedures for adjudicating serious adverse events and cause of death in your Adjudication Committee charter.

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

BADRUL A CHOWDHURY
12/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383 **INFORMATION REQUEST**

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We also refer to your September 28, 2010 submission, received on October 1, 2010, containing your response to our Complete Response Letter dated, October 16, 2009.

During our preliminary review of your complete response, we identified the following potential review issues:

1. No regulatory paradigm exists for the use of two doses of a long acting beta agonist (LABA) for bronchodilatory effect. It is unclear whether the role for two doses is supported or, specifically, adequate data has been submitted to support a clinically meaningful efficacy or safety advantage of a higher dose over a lower dose.

2. You have requested a claim that Arcapta Neohaler improves the St. George's Respiratory Questionnaire score: *"Arcapta Neohaler 150 mcg resulted in a significantly lower (improved) mean SGRQ total score compared to placebo."* The data submitted in support of this claim, adequacy of the duration of the trials and the variability that exists amongst the key efficacy trials will be review issues.

3. You have requested an onset of action claim: "*onset of action within 5 minutes*." The definition of onset of action and data in support of this claim will be review issues.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are

preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

To facilitate our review, we have the following requests for information.

Clinical Pharmacology

4. Submit SAS transport files, containing identification, treatment, dose, individual concentrations, and individual pharmacokinetic (PK) parameters for the PK study: CQAB1492101.

Statistical

5. On page 61 of the clinical study report CQAB149B2223, Table 11-3 and Table 11-4, summarize the statistical analysis of trough FEV1 and time-standardized AUCs on days 15/16 (PD analysis set). The tables are provided below for your reference. Provide the programs used to generate the tables and include the input datasets.

Table 11-3 Summary of the statistical analysis of change from baseline in trough FEV_1 and time-standardized AUCs on days 15/16 (PD analysis set)

		Change from baseline		
PD parameter	**Treatment**	**Mean**	**Lower 90% CI**	**Upper 90% CI**
Trough FEV_1 (L)	37.5 µg b.i.d	0.156	0.083	0.228
	75 µg q.d	0.197	0.125	0.269
	150 µg q.o.d	0.199	0.125	0.272
	Placebo	-0.005	-0.080	0.071
AUC 0-24h (L)	37.5 µg b.i.d	0.196	0.127	0.266
	75 µg q.d	0.198	0.127	0.269
	Placebo	0.030	-0.044	0.103
AUC 0-48h (L)	75 µg q.d	0.218	0.148	0.288
	150 µg q.o.d	0.198	0.135	0.260
	Placebo	0.059	-0.012	0.129
AUC 24-48h (L)	75 µg q.d	0.216	0.144	0.288
	150 µg q.o.d	0.201	0.138	0.265
	Placebo	0.085	0.013	0.156

Source: PT-Table 14.2-2.1

A secondary analysis was performed on these PD variables providing all two-way contrasts between the treatments (PT-Table 14.2-2.4). The contrasts with placebo on day 15/16 are shown in Table 11-4.

Table 11-4 Summary of the statistical analysis of contrasts with placebo for change from baseline in trough FEV_1 and time-standardized AUCs on days 15/16 (PD analysis set)

		Contrast with placebo		
PD parameter	**Treatment**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
Trough FEV_1 (L)	37.5 µg b.i.d	0.160	0.036	0.284
	75 µg q.d	0.202	0.077	0.327
	150 µg q.o.d	0.203	0.077	0.329
AUC 0-24h (L)	37.5 µg b.i.d	0.167	0.046	0.287
	75 µg q.d	0.168	0.046	0.291
AUC 0-48h (L)	75 µg q.d	0.159	0.040	0.279
	150 µg q.o.d	0.139	0.026	0.252
AUC 24-48h (L)	75 µg q.d	0.131	0.009	0.253
	150 µg q.o.d	0.117	0.002	0.231

Source: PT-Table 14.2-2.4

Chemistry, Manufacturing and Controls

6. Agree to reassess and revise, as appropriate, the acceptance criteria for lactose impurities, once a sufficient number of batches (e.g., ≥ten) are tested using the new reporting limit of (b) (4). Propose acceptance criteria that are reflective of the data obtained. The limited data for three batches of lactose provided thus far do not support the permissive limit of up to (b) (4) total impurities in lactose, with all having less than (b) (4) totals.

7. Revise the HOW SUPPLIED section of the package insert to more accurately describe the blister cards, e.g., "Box of 30 (5 blister cards with 6 capsules each)."

8. Revise the SPL style sheets for both strengths to list the lactose monohydrate as an inactive ingredient.

9. (b) (4) the drug product, when exposed to the ICH Q1B photostability stress conditions, which is also reflected in the STORAGE AND HANDLING section of the package insert.

Please provide your response to our request for information by COB on December 15, 2010. If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

CAROL F HILL
12/08/2010

BADRUL A CHOWDHURY
12/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Carol RPM/ODE II/DPARP 301-796-1226	
DATE December 6, 2010	IND NO.	NDA NO. 22383	TYPE OF DOCUMENT NDA Resubmission	DATE OF DOCUMENT October 1, 2010
NAME OF DRUG Arcapta Neohaler (indacaterol maleate)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG Beta 2 Agonist	DESIRED COMPLETION DATE February 11, 2010

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: We request a review of the carton and container, package insert, medication guide, patient instructions for use, and proposed REMS included in the 9/28/10 submission in the EDR.

Mid-Cycle Meeting: [1/11/11]

Labeling Meetings: [1/11/11]

Wrap-Up Meeting: [1/28/11]

SIGNATURE OF REQUESTER Carol Hill	METHOD OF DELIVERY (Check one) ☑MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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
12/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Carol Hill/RPM, ODE II/DPARP 301-796-1226

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
December 6, 2010		22383	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Arcapta Neohaler	Standard	Beta2-Agonist	February 11, 2011

NAME OF FIRM:	
Novartis	PDUFA Date: April 1, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☑ PACKAGE INSERT (PI)
☑ PATIENT PACKAGE INSERT (PPI)
☑CARTON/CONTAINER LABELING
☑ MEDICATION GUIDE
☑INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☑ORIGINAL NDA/BLA (RESUBMISSION)
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
☑ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\cdsesub1\EVSPROD\NDA022383\\0027\m1\us\proposed.pdf
Submission is dated September 28, 2010 in the EDR.

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: We request a review of the carton and container, package insert, medication guide, patient instructions for use, and proposed REMS included in the 9/28/10 submission in the EDR.

Mid-Cycle Meeting: [1/11/11]

Labeling Meetings: [1/11/11]

Wrap-Up Meeting: [1/28/11]

SIGNATURE OF REQUESTER
Carol Hill

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☑eMAIL ☐ HAND

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
12/06/2010

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

FACSIMILE TRANSMITTAL SHEET

DATE: November 5, 2010

To: Ann Shea Director, Drug Regulatory Affairs	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy and Rheumatology Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-2300

Subject: NDA 22383 - Clinical Pharmacology Information Request

Total no. of pages including cover: 3

Comments: Please acknowledge receipt

Document to be mailed: YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22383
Novartis Pharmaceuticals Corporation
Arcapta Neohaler

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler (indacaterol maleate) Inhalation Powder.

We also refer to your September 28, 2010, submission, containing your response to our October 16, 2009, Complete Response action letter.

We are reviewing your submission and have the following requests for information.

1. Provide all datasets, programs and outputs for the dose-response analyses modeling report "Update of the bronchodilatory dose-response analysis of indacaterol in COPD".

2. Use the following instructions when submitting the requested information.

    a. Submit all datasets used for model development and validation as SAS transport files (*.xpt).

    b. Provide a description of each data item in a Define.pdf file.

    c. Submit model codes or control streams and output listings as ASCII text files with the (*.txt) file extension.

Provide your response to this request no later than COB on November 12, 2010. If you have any questions, call Carol Hill, Regulatory Health Project Manager, at (301) 796-1226.

Drafted: chill/November 1, 2010
Clearance History: Barnes/November 4, 2010
Lee/November 5, 2010
Wang/November 5, 2010
Finalized: chill/November 5, 2010

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
11/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022383 **ACKNOWLEDGE CLASS 2 RESPONSE**

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

Attention: Ann Shea
Director, Drug Regulatory Affairs

Dear Ms. Shea:

We acknowledge receipt on October 1, 2010 of your, September 28, 2010, resubmission to your new drug application for Arcapta Neohaler, (indacaterol maleate) inhalation powder, 75 and 150 mcg.

We consider this a complete, class 2 response to our, October 16, 2009, action letter. Therefore, the user fee goal date is April 1, 2010.

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

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CPMS
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

CAROL F HILL
10/07/2010
Signed for Sandy Barnes

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22383 **DISCIPLINE REVIEW LETTER**

Novartis Pharmaceuticals, Inc.
One Health Plaza
East Hanover, NJ 07936

Attention: Ann Shea
Senior Associate Director, Drug Regulatory Affairs

Dear Ms. Shea:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta Neohaler (indacaterol maleate) inhalation powder, 150 and 300 mcg.

This letter is to notify you that we are cancelling the labeling teleconference scheduled for September 14, 2009, from 1:30-2:30 pm. During the ongoing review of the indacaterol application for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) we have identified certain deficiencies and determined that the deficiencies preclude discussion of labeling at this time. Those deficiencies include:

1. You have not adequately demonstrated a dose or doses of indacaterol that is both safe and efficacious for the treatment of bronchospasm associated with COPD. Data from study B2335s suggest that indacaterol at doses of 75-300 µg once daily elicit a similar FEV1 response compared to placebo. However, the long-term safety of indacaterol at the proposed doses of 150 and 300 µg has not been determined. In the 12 month safety study (B2334), COPD patients who received indacaterol at doses of 300 µg and 600 µg once daily had more combined cardiac and/or cerebrovascular (CCV) serious adverse events than those who received placebo or the marketed long-acting beta-2 agonist, formoterol (3.4%, 2.6%, 1.4%, and 0.9% for indacaterol 300 µg, 600 µg, formoterol and placebo, respectively). The long-term safety of indacaterol at doses less than 300 µg has not been evaluated.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Supervisory CPMS
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

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

/s/

SANDRA L BARNES
09/11/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 31, 2009

TO: Ann Shea of Novartis

THROUGH : Carol Hill/email

FROM: Timothy Robison, PhD, DABT

SUBJECT: Non-clinical Information Request

APPLICATION/DRUG: NDA 22-383/Arcapta Neohaler (indacaterol)

Content of the Email dated, July 31, 2009

For the 26-week carcinogenicity study with TgrasH2 mice, uterine endometrial stromal polyps were observed for 3 of 25 female TgrasH2 mice in the 600 mg/kg/day group. Provide the background incidence of uterine endometrial stromal polyps in female TgrasH2 mice. Please provide your response by email or fax by COB EST on Monday, August 3, 2009 or at the latest by 9:00am on Tuesday, August 4, 2009. Also formally submit your response to the application.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22383	ORIG 1	NOVARTIS PHARMACEUTICALS CORP	INDACATEROL

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
07/31/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-383

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 18, 2008, received December 18, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Indacaterol Maleate Inhalation Powder, 150 mg and 300 mg.

We also refer to your April 28, 2009, correspondence, received April 28, 2009, requesting review of your proposed proprietary name, Arcapta Neohaler. We have completed our review of the proposed proprietary name, Arcapta Neohaler, and have concluded that it is acceptable.

The proposed proprietary name, Arcapta Neohaler, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 28, 2009, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sean Bradley, Regulatory Safety Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1332. For any other information regarding this application contact OND Regulatory Project Manager in the Division of Pulmonary and Allergy Products.

Sincerely,

{See appended electronic signature page}

Carol Holquist, R.Ph.
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

```
 /s/
----------------------
Carol Holquist
7/23/2009 12:15:42 PM
```

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Division of Cardiovascular and Renal Products-QT IRT Team	Carol Hill, PM, x1226 Division of Pulmonary and Pulmonary Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 21, 2009		22-383		December 15, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Arcapta Neohaler (indacaterol)		LABA	August 28, 2009

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- × OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a request for review of the QT study contained in the NDA submission dated December 15, 2008. This submission is electronic and may be found in the EDR under the same date.

PDUFA Due Date: October 18, 2009

SIGNATURE OF REQUESTER Carol Hill	METHOD OF DELIVERY (Check one) × MAIL ☐ HAND
SIGNATURE OF RECEIVER Devi Kozeli	SIGNATURE OF DELIVERER See electronic signature

---

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
7/21/2009 06:43:46 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **May 29, 2009**

To: **Ann Shea** **Sr. Assoc. Dir., Drug Regulatory Affairs**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals Corp.**	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: **NDA 22-383: Revised Clinical Pharmacology Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22-383
Novartis Pharmaceuticals Corporation
Indacaterol

We are in the process of reviewing your new drug application (NDA) dated, December 15, 2008, and have the following requests regarding the datasets of the bronchodilatory dose-response and frequency of dosing for indacaterol in the Modeling Report (release date: 24-Apr-2009).

1. Provide all datasets which were used for the Bayesian meta-analysis

2. Provide all datasets which were used for the peak-to-trough ratio analysis.

3. Provide full program (S-plus) which was used for NLME analysis.

Please disregard the information request sent today by email on May 29, 2009 at 3:47 pm. If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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
5/29/2009 05:22:19 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **May 29, 2009**

To: **Ann Shea** **Sr. Assoc. Dir., Drug Regulatory Affairs**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals Corp.**	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: **NDA 22-383: Clinical Pharmacology Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22-383
Novartis Pharmaceuticals Corporation
Indacaterol

We are in the process of reviewing your new drug application (NDA) dated, December 15, 2008, and have the following requests regarding the datasets for the report in Appendix-2-dose-response-and-regimen-modeling.

1. Provide all datasets which were used for the Bayesian meta-analysis

2. Provide all datasets which were used for the peak-to-trough ratio analysis.

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

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
5/29/2009 03:43:10 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **April 11, 2009**

To: **Fernando Marcella, M.S.** **Drug Regulatory Affairs-GR CMC**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals Corp.**	Division of Pulmonary and Allergy Products
Fax number: 973-781-3320	**Fax number:** 301-796-9728
Phone number: 862-778-5062	**Phone number:** 301-796-1226

Subject: **NDA 22-383 – CMC Information Request**

Total no. of pages including cover: **3**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22-383
Novartis Pharmaceuticals Corporation
Arcapta (b) (4)

We are in the process of reviewing your amendment dated, March 31, 2008 and we have the following preliminary comments and requests.

1. Provide report IDD00483A which provides details of the investigation of how non-optimal capsule piercing affects the pharmaceutical performance of the drug product. Without this information it is not possible for us to completely gauge the results of the study of the 21 complaint devices returned from the trials.

(b) (4)

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

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
4/11/2009 11:41:10 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: **April 2, 2009**

To: **Ann Shea, Sr. Assoc. Dir. Regulatory Affairs**	**From:** Carol Hill, M.S. Regulatory Health Project Manager
Company: **Novartis Pharmaceuticals**	Division of Pulmonary and Allergy Products
Fax number: 973-781-2565	**Fax number:** 301-796-9728
Phone number: 862-778-4567	**Phone number:** 301-796-1226

Subject: **NDA 22-383 – Statistical Information Request**

Total no. of pages including cover: **1**

Comments: **Please acknowledge receipt.**

Document to be mailed: ☐ **YES** ☑ **NO**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

NDA 22-383
Novartis Pharmaceuticals
Indacaterol

Please refer to your submission dated, December 20, 2006 for IND 48,649. In our February 1, 2007, response, to your request for a special clinical protocol assessment for study QAB149B2335s, additional comment (b) specifically stated:

> *Some subjects will be treated with study medication for longer than two weeks prior to making the decision regarding dose selection for stage two. Additional safety and efficacy information will be obtained on these subjects during that time period. Following dose selection, subjects participating in the two dose groups that are not carried forward will be discontinued from further participation in the study. Assure that your study report includes a summary of the additional efficacy and safety data (beyond the two week time point) for these subjects who are discontinued.*

You responded, February 21, 2007 with the following comment:

> *Novartis agrees to include a summary in the study report of the additional efficacy and safety data (beyond the two week time point) for these subjects who are discontinued.*

We were unable to locate this summary in the clinical study report, for QAB149B2335s, included in your NDA submission. If it is included in the NDA submission, indicate the specific section and page number for this summary; if it is not included, provide this report. Summarize the data at the following time points: Day 2, Day 15, Day 29, Day 57, Day 85, Day 113, Day 148, and Day 182. Also include a summary of trough FEV_1 and FEV_1 $AUC_{(1\text{-}4h)}$. A similar output as the one in your response submitted on March 16, 2009 would be appropriate.

Please submit your response by COB on April 6, 2009 via email to carol.hill@fda.hhs.gov or fax at 301-796-9728. If you have any questions, contact Carol Hill, Regulatory Health Project Manager at 301-796-1226.

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
4/2/2009 02:15:26 PM
CSO

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

Memorandum of Facsimile Correspondence

Date: March 23, 2009

To: Ann Shea

Company: Novartis Pharmaceuticals Corporation

Fax: TBD

Phone: 862-778-4567

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-383; Response to Clarifying Questions

# of pages: 3

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 22-383
Indacaterol
Novartis

Please see the response below to your March 9, 2009, email request for clarification to the February 27, 2009, FDA filing communication sent on March 2, 2009:

Sponsor Question:

Novartis only seeks the approval of QAB for COPD indication. All the asthma studies that were conducted with QAB in the early drug development were submitted to the NDA 22-383. Could you please clarify this request?

Does the Agency want the SAS transport files or CRTs or neither of these for the relevant asthma studies?

FDA Response:

While we acknowledge that Novartis is seeking approval of QAB at this time for a COPD indication only, we believe for a beta agonist that will likely be used in patients with asthma as well as COPD, it is important to look at available dose response and dosing interval data that is available for asthma patients as well. Submission of summary data for QAB from the asthma clinical trials (rather than looking at each asthma trial individually) by Novartis would facilitate the review process significantly.

We do not need SAS files or CRTs at this time

If you have any questions, please contact Carol Hill at 301-796-1226.

_____
Eunice H. Chung, Pharm.D.
Regulatory Project Manager

NDA 22-383
Indacaterol
Novartis

Drafted: EChung/9MAR2009
Initialed: SBarnes/20MAR2009
LWu/23MAR2009
ADurmowicz/23MAR2009

Finalized: EChung/23MAR2009

Cc: Carol Hill

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

/s/

Eunice Chung
3/23/2009 04:04:39 PM
CSO
on behalf of Carol Hill

Eunice Chung
3/23/2009 04:05:03 PM
CSO
on behalf of Carol Hill

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

Memorandum of Facsimile Correspondence

Date: March 23, 2009

To: Ann Shea

Company: Novartis Pharmaceuticals Corporation

Fax: TBD

Phone: 862-778-4567

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-383; Statistical Information request #2

# of pages: 3

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 22-383
Indacaterol
Novartis

We are currently reviewing your December 15, 2009, New Drug Application 22-383 and have the following requests:

1. On page 54, section 2.7.3 Summary of clinical efficacy, you presented table 3-21 (attached below). The second part of the table provides only the summary of FEV_1 $AUC_{(1\text{-}4h)}$, submit an expansion of that information.

    a. Provide summaries for all study arms at all time points when FEV_1 $AUC_{(1\text{-}4h)}$ is available, including comparisons between all possible pairs of treatment arms in a similar format as the results you presented in the March 16, 2009, response submitted on to our March 9, 2009, statistical information request.

2. Indicate which data set was used to generate the table. We were only able to find "AUC_0_4" evaluated at time points: "Week 1 Day 1", "Week 2 Day 14", "Week 12 Day 84", and "Week 26 Day 182" in data set "B2335s\a_spider.xpt".

Table 3-21 Study B2335S Key interim analysis results at Day 15 (imputed with LOCF): treatment comparisons (interim ITT population)

		Treatment			Treatment difference		
Treatment	**N**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**
Trough FEV_1 (L)							
Comparisons with placebo							
Ind 75 µg	104	1.46	0.024	Ind 75 µg - Placebo	0.15	0.029	(0.09, 0.20)
Ind 150 µg	105	1.49	0.024	Ind 150 µg - Placebo	0.18*	0.029	(0.12, 0.24)
Ind 300 µg	110	1.52	0.024	Ind 300 µg - Placebo	0.21*	0.029	(0.15, 0.27)
Ind 600 µg	108	1.51	0.024	Ind 600 µg - Placebo	0.20	0.029	(0.14, 0.25)
For	105	1.42	0.024	For - Placebo	0.11	0.029	(0.06, 0.17)
Tio	112	1.45	0.023	Tio - Placebo	**0.14**	0.028	(0.08, 0.19)
Placebo	104	1.31	0.024				
AUC 1h-4h FEV_1 (L)							
Comparisons with placebo							
Ind 75 µg	95	1.50	0.034	Ind 75 µg - Placebo	0.20	0.032	(0.14, 0.27)
Ind 150 µg	96	1.53	0.034	Ind 150 µg - Placebo	0.23*	0.032	(0.16, 0.29)
Ind 300 µg	99	1.58	0.034	Ind 300 µg - Placebo	0.28*	0.031	(0.22, 0.34)
Ind 600 µg	97	1.53	0.034	Ind 600 µg - Placebo	0.23	0.031	(0.17, 0.29)
For	93	1.52	0.035	For - Placebo	**0.22**	0.032	(0.16, 0.28)
Tio	99	1.49	0.034	Tio - Placebo	0.19	0.031	(0.13, 0.25)
Placebo	90	1.30	0.033				

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center(country), with center(country) as a random effect.
Bold LS mean differences were those identified as reference values by dose selection criteria, * = selected doses
Source: [Study B2335S-Table 11-5]

NDA 22-383
Indacaterol
Novartis

Please submit your response by March 27, 2009 COB via email to Carol.hill@fda.hhs.gov or via fax at 301 796-9718. If you have any questions, please contact Carol Hill at 301-796-1226.

_____
Eunice H. Chung, Pharm.D.
Regulatory Project Manager

NDA 22-383
Indacaterol
Novartis

Drafted: EChung/18MAR2009
Initialed: SBarnes/20MAR2009
DLiu/23MAR2009
QLi/23MAR2009

Finalized: EChung/23MAR2009

Cc: Carol Hill

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

/s/

Eunice Chung
3/23/2009 03:50:02 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 22-383

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

Attention: Ting Chen, MS
Director, Drug Regulatory Affairs

Dear Ms. Chen:

Please refer to your New Drug Application (NDA) dated December 18, 2008, received December 18, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for indacaterol maleate inhalation powder, QAB149.

We also refer to your December 19, 2008, correspondence, received December 19, 2008, requesting review of your proposed proprietary name, Arcapta (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reason.

(b) (4)

Additionally, during our evaluation of the proposed proprietary name, Arcapta (b) (4), we evaluated the root name, Arcapta. Our findings indicate that the name Arcapta, without the term (b) (4) did not appear to be vulnerable to name confusion that could lead to medication errors. Thus, we propose you consider the use of the name Arcapta without "(b) (4)" for this product.

If you choose to use the proposed proprietary name, Arcapta, please re-submit a name request for this proposed name. However, if you intend to use an alternative proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, HTTP://www.fda.gov/cder/guidance/7935dft.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sean Bradley, Regulatory Safety Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1332. For any other information regarding this application contact Carol Hill, Regulatory Project Manager in the Division of Pulmonary and Allergy Products.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
3/18/2009 03:57:14 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-383 **DISCIPLINE REVIEW LETTER**

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07636-1080

Attention: Ting Chen, M.S.
Director, Regulatory Affairs

Dear Ms. Chen:

Please refer to your December 15, 2008, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arcapta (b) (4) (Indacaterol Maleate Inhalation Powder).

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

The following comments pertain to the drug substance.

1. With respect to the (b) (4) at Novartis Pharma AG site:

   a. Provide an explanation for its use.

   b. Provide the amount used.

   c. Provide the identity of this material, or provide a letter of authorization to allow our reference to a master file containing this pertinent information.

2. Provide the micronization parameters that are used for (b) (4) the drug substance.

3. Provide, or give reference to the pertinent section of the application that includes, the acceptance criteria that are applied to recovered (b) (4) of the drug substance (S.2.2.4.3.9). These could not be located in S.2.3.

4. Revise the description of the drug substance manufacturing process so that all points at which recovered (b) (4) are used, are identified.

5. Provide a representative certificate of analysis for the (b) (4) final indacaterol maleate.

6. As the purification of (b) (4)

7. Provide a brief description of how the single (b) (4) .

8. Revise the method 10331.01 *Particle size by laser light diffraction* to indicate the equipment (measuring and dispersing devices) that will be used for the routine collection of data. Due to the importance of the method, it is not acceptable to merely give examples of these items, which are often unique and which produce particle size distribution data distinct from that obtained with alternate equipment. Switching reagents and equipment would require a study of comparability or might necessitate a change of the acceptance criteria.

9. For method 10331.01, clarify whether or not the (b) (4) the validation study. If not, provide data demonstrating how the use of this agent impacts the PSD results obtained with the method.

10. Modify the method 20901.01 *Identity by X-ray Diffraction* such that it specifies that a (b) (4) will be used, as per the statements made in the introduction of the method validation report VR20901A. Alternately, specify another (b) (4) identity testing.

11. Revise the method 32001.01 *Enantiomer by HPLC* used for the determination of the enantiomer (b) (4) content in the drug substance to include the shelf lives of the various solutions and standards, consistent with what was found in the validation studies.

12. Revise the method 35601.01 (b) (4) in the drug substance to include the shelf lives of the various solutions and standards, consistent with what was found in the validation studies.

13. Revise the system suitability criteria for the method 35601.01 such that the requirements are a more reasonable reflection of the capability demonstrated by the data in the validation report VR35601B.

14. Revise the method 35602.01 (b) (4) in the drug substance to include the shelf lives of the various solutions and standards, consistent with what was found in the validation studies.

15. Revise the system suitability criteria for the method 35602.01 such that the requirements are a more reasonable reflection of the capability demonstrated by the data in the validation report VR35611C.

16. For the method 36911.01 *Heavy metals by ICP-OES*:

    a. Revise the system suitability criteria for precision (not more than (b) (4) of the analyte measurements for the calibration check solution to reflect the precision that is demonstrated in the validation report VR36911B.
    (b) (4)

17. Additional comments regarding the acceptance criteria and reporting limit for (b) (4) may be forthcoming pending review by the pharmacology/toxicology team.

18. For the drug substance method 54001.01 *Impurities and assay by HPLC* (b) (4) relative standard deviation (RSD) for the replicate injections (n = 6) of reference solution 2, considering the repeatability data in the validation report VR30001C.

19. For method 54001.01, include the use of the response factor for the potential impurity (b) (4) for unspecified impurities.

20. Revise method 54001.01 to include direction regarding the sample and reference solution shelf-lives.

21. (b) (4) Provide an agreement to revisit this acceptance criterion and revise it appropriately once a sufficient number of batches of drug substance are prepared with the commercial process on production equipment.

22. Based on the data provided for the batches of drug substance prepared with the (b) (4) process on production equipment (July-August 2008 batches), the acceptance criteria for related substances are considered to be too permissive. However, since the number of these batches is limited, provide an agreement to revisit these acceptance criteria and revise as appropriate once a sufficient number of batches of drug substance are prepared with the commercial process on production equipment.

23. Set acceptance criteria for (b) (4) in the drug substance that are more closely reflective of what your production process routinely achieves, as there is no therapeutic benefit to the patient from (b) (4), nor has it been shown that (b) (4) levels approaching your proposed acceptance criteria do not impact drug substance stability or drug product performance or stability.

The following comments pertain to the drug product.

24. DMF (b) (4) was reviewed and was found to be inadequate to support your application. A deficiency letter was forwarded to the holder.

25. Provide an agreement to revisit and revise, if appropriate, the device extractables acceptance criteria for the (b) (4) release agent once you have collected data from multiple commercial scale device batches.

26. Provide the report on the complaint investigations for the phase III drug product as indicated in section P.2.4.3.7.

27. Revise the reporting limit for related substances in the lactose to more closely reflect the true limit of quantitation. The data in the validation report are supportive of a limit of quantitation that is much lower than the 0.3% limit currently in use.

28. Provide data and rationale for your justification of the reporting limit of (b) (4) for the three unknown impurities in the lactose excipient (b) (4)).

29. Propose an acceptance criterion for the total impurities allowed in lactose and base it on data from batches that have been used in preparing the phase 3 clinical material and registration stability batches. Provide these data along with the revised impurities acceptance criteria.

30. Provide the numerical impurities data in tabular format for the seventeen batches of lactose that were said to be used to set the acceptance criteria for impurities and related substances and indicate what these batches of lactose were used for in the development program (e.g., preparation of phase 3 clinical batches, preparation of phase 1 clinical batches, preparation of registration stability batches).

31. (b) (4) the acceptance criteria for the particle size by laser diffraction for the lactose excipient. Based on the representative data provided (n = 5 batches) in the justification of specifications section, the limits for (b) (4), and the span are excessive. Provide the particle size laser diffraction data for

the lactose used to prepare the clinical and registration stability batches along with the revised acceptance criteria.

32. Provide performance data (dose delivery and APSD) for batches of drug product prepared with lactose having (b) (4) content up to (b) (4), the maximum amount said to have been observed in the seventeen representative lactose batches used to set the (b) (4) content limit of NMT (b) (4). Without such data it is unknown whether or not there are any consequences in terms of the drug product performance. Alternately, lower the acceptance criteria to the quantitation limit (i.e., not more than (b) (4)), as most of the batches were not observed to have detectable (b) (4) lactose.

33. Based on the representative data provided in the section on justification of lactose specifications, (b) (4) the acceptance criterion for protein content to not more than (b) (4)).

34. The validation report VR32001K for method 32001.01 *Enantiomer by HPLC* for the drug product did not address the potential for interference from the three specified drug substance impurities, (b) (4) . Provide data demonstrating the specificity of the method and the ability to assess the amount of (b) (4) in the presence of any of these drug substance impurities.

35. Comments regarding the acceptance criteria for foreign particulates in the drug product determined by method 37321.01 *Light obscuration particle count* may be forthcoming, depending on the evaluation of our pharmacology/toxicology team.

36. Provide the results of specificity studies for the method 59701.01 *Assay and uniformity of dosage units by content uniformity by HPLC* to demonstrate the discrimination of the analyte in the presence of impurities (degradants, by-products).

37. Revise the method 50211.01 *Delivered-Dose Uniformity by HPLC* to remove the allowance of a (b) (4) excessive with respect to the typical volume of air withdrawn through such products by patients during use.

38. The validation report VR50211D *Content uniformity of delivered dose by HPLC* contains data showing both strengths delivering well below the target deliveries of (b) (4). In fact, with a mean delivery of (b) (4) observed for the (b) (4) strength, the proposed acceptance criterion of (b) (4) of the target is not achieved. Provide an explanation or reference the part of the application containing an explanation for this observed low emitted dose delivery, when compared to other batch analyses data provided (e.g., in P.5.4).

39. For the method 10351.01 *Aerodynamic particle size distribution by Andersen Cascade Impactor*, clarify how results would be assessed relative to the specification acceptance criteria if mass balance requirements were not met for any individual test and repeat tests (up to two) were performed. This was not clear from the "material balancing, averaging and reporting or results" section of the method.

40. Revise the method 10351.01 to remove the allowance of a second (b) (4) is excessive with respect to the typical volume of air withdrawn through such products by patients during use.

41. DMF (b) (4) for the information supporting the manufacture of the Concept1 device was reviewed and was found to be inadequate. A deficiency letter was forwarded to the holder.

42. Provide justification for the allowance of up to (b) (4) of force to open and close the mouthpiece, with consideration given to the ranges that were measured with device samples from batch B1320 presented in the application.

43. Provide conformation that the photostability studies performed on the drug product dosage form used a light source that was consistent with the recommendations of ICH Q1B. Provide justification if the source deviated from those recommendations.

44. Provide data for more than one batch of devices (b) (4)

45. Revise the method validation package to include a list of samples that includes the impurity (b) (4) since it is needed for the assurance of sufficient resolution for both the drug substance and drug product impurities methods. Samples of (b) (4) should be provided if a request for samples is made by Agency laboratories.

46. Specify the type of lactose used to prepare the placebo capsules and provide the specification to which it is tested.

47. If revisions are made to various sections of the application in response to the comments above, include these revised sections in appendices to the response with flags identifying the changes made.

48. We have the following preliminary labeling comments.

a. Revise the DESCRIPTION section of the labeling as follows: Each clear, hard gelatin capsule contains a dry powder blend of (b) (4) indacaterol (b) (4) with approximately 25 mg of lactose monohydrate (which contains trace levels of milk proteins) as the carrier.

b. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the package insert to include a brief description of the appearance of the device.

c. Revise the section of the med-guide entitled "How do I store Arcapta (b) (4)?" to specifically state that both the inhaler and the blister-packaged capsules should be protected from moisture and heat and be stored at room temperature.

d. Revise the section of the med-guide entitled ' (b) (4)" such that it is clear that the "Arcapta (b) (4)" refers to the complete drug product, i.e., the inhaler and the blister-packaged capsules.

e. Revise the med-guide section to include a clear, separate, and specific warning to patients to only open the blister packaging immediately before they are to administer a capsule for inhalation. The current statements under the "Remove an Arcapta capsule" do not emphasize this point in a strong enough manner. Also, revise the "Remember:" section adding a statement to the same effect, e.g. "CAPSULES SHOULD ALWAYS BE STORED IN THE BLISTER, AND ONLY REMOVED IMMEDIATELY BEFORE USE."

f. The established name and the product strength must match. Therefore, you have the following two options:

i. Change the established name of the drug product to indacaterol inhalation powder while retaining the strength (b) (4) and include footnotes stating, respectively, (b) (4) or

ii. Change the (b) (4) while retaining the established name as indacaterol maleate inhalation powder, in which case no additional statement is needed.

g. (b) (4)

h. Revise the dosage form in the SPL style sheets to "powder, metered" from "inhalant."

i. Revise the SPL style sheet for the (b) (4) strength such that the amount of lactose per capsule is 25 mg.

49. Provide the expected introduction concentration (EIC) of the active moiety entering the aquatic environment from patient use. If the calculation of the EIC differs from that recommended in the Agency guidance entitled *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications*, provide the calculations for our review and evaluation.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Eunice Chung, Project Management Staff, at (301) 796-4006.

Sincerely,

Ali Al-Hakim, Ph.D.
Chief, Branch II
Division of Premarketing I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Ali Al-Hakim
3/11/2009 02:31:58 PM

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

Memorandum of Facsimile Correspondence

Date: March 9, 2009

To: Ting Chen, MS
Director
Drug Regulatory Affairs

Company: Novartis

Fax: 973-781-2565

Phone: 862-778-1530

From: Eunice Chung, Pharm.D.
Regulatory Project Manager
Division of Pulmonary and Allergy Products

Subject: NDA 22-383; Statistical Information Request

# of pages: 3

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you received this document in error, please immediately notify us by telephone at (301) 796-2300 and return it to us at FDA, 10903 New Hampshire Ave, Building 22, DPAP, Silver Spring, MD 20993.

Thank you.

NDA 22-383
Indacaterol
Novartis

We are currently reviewing your December 15, 2008, New Drug Application (NDA) and have the following request:

> In the table attached from section 2.7.3 Summary of clinical efficacy you commented:
>
> > *At 14 days, the pharmacodynamic effect is stable, with no evidence of an improved effect with longer dosing periods, as shown in table 3-24 from study B2335s. Thus the data at 14 days are a reliable basis for dose selection.*
>
> We would like to see an expanded table with information on all study arms, i.e. Ind 75µg, Ind 150µg, Ind 300µg, Ind 600µg, Formoterol, Tiotropium, and placebo at 4 time points: day 2, day 15, week 12, and week 26. Please use trough FEV_1 with imputation and without imputation (using available FEV1 only). Other than the number of patients (N) you already included in the table with the LOCF imputation approach, please add one more column to indicate the number of patients without imputation.

Please submit your response to my attention via facsimile to 301-796-9718 or via email to Eunice.Chung@fda.hhs.gov by COB on March 16, 2009. Your response will need to be submitted officially to the NDA as well.

Table 3-24 Study B2335S Trough FEV_1 (L) at Day 2, Day 15, and Week 26 (imputed with LOCF): treatment comparisons (ITT population)

	Treatment				Treatment difference			
Treatment	**N**	**LS mean**	**SE**	**Comparison**	**LS mean**	**SE**	**95% CI**	**p-value**
Day 2								
Comparisons for superiority to placebo (1)								two-sided
Ind 150 µg	400	1.44	0.011	Ind 150 µg - Placebo	0.11	0.012	(0.08, 0.13)	<.001
Ind 300 µg	396	1.48	0.011	Ind 300 µg - Placebo	0.14	0.012	(0.12, 0.16)	<.001
Tio	395	1.43	0.011	Tio - Placebo	0.10	0.012	(0.07, 0.12)	<.001
Placebo	391	1.34	0.011					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.01	0.012	(-0.01, 0.03)	<.001
				Ind 300 µg - Tio	0.04	0.012	(0.02, 0.07)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	0.03	0.012	(0.01, 0.06)	0.006
Day 15 (imputed with LOCF)								
Comparisons for superiority to placebo (1)								two-sided
Ind 150 µg	389	1.47	0.013	Ind 150 µg - Placebo	0.17	0.015	(0.14, 0.20)	<.001
Ind 300 µg	391	1.48	0.013	Ind 300 µg - Placebo	0.18	0.015	(0.15, 0.21)	<.001
Tio	393	1.43	0.013	Tio - Placebo	0.14	0.015	(0.11, 0.17)	<.001
Placebo	377	1.29	0.013					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.03	0.015	(0.01, 0.06)	<.001
				Ind 300 µg - Tio	0.04	0.015	(0.02, 0.07)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	0.01	0.015	(-0.02, 0.04)	0.461
Week 26 (imputed with LOCF)								
Comparisons for superiority to placebo (1)								two-sided
Ind 150 µg	349	1.41	0.017	Ind 150 µg - Placebo	0.16	0.019	(0.12, 0.19)	<.001
Ind 300 µg	361	1.44	0.017	Ind 300 µg - Placebo	0.18	0.018	(0.14, 0.22)	<.001
Tio	356	1.40	0.017	Tio - Placebo	0.14	0.018	(0.10, 0.18)	<.001
Placebo	317	1.26	0.017					
Comparisons for non-inferiority to tiotropium (2)								one-sided
				Ind 150 µg - Tio	0.02	0.018	(-0.02, 0.05)	<.001
				Ind 300 µg - Tio	0.04	0.018	(0.00, 0.07)	<.001
Other comparisons								two-sided
				Ind 300 µg - Ind 150 µg	0.02	0.018	(-0.01, 0.06)	0.204

LS mean = least squares mean, SE = standard error of the mean, CI = confidence interval.
Mixed model: Trough FEV_1 = treatment + baseline FEV_1 + FEV_1 reversibility components + smoking status + country + center (country), with center(country) as a random effect.
Superiority to placebo means that the two-sided $p < 0.05$ and the 95% CI is entirely higher than 0 L.
Non-inferiority to tiotropium means that the one-sided $p < 0.025$ and the 95% CI is entirely higher than -0.055 L.
-15 min time point is equal to 23h 45min as measured at Visit 14 after 26 weeks treatment prior to final dose.
Source: [Study B2335S-Table 11-9]

If you have any questions, please contact Eunice H. Chung at 301-796-4006.

Eunice H. Chung, Pharm.D.
Regulatory Project Manager

NDA 22-383
Indacaterol
Novartis

Drafted: EChung/March 9, 2009
Initialed: SBarnes/March 9, 2009
DLiu/ March 10, 2009
QLi/March 10, 2009

Finalized: Robinson for EChung/March 11, 2009

Cc: Carol Hill

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

/s/

Angela Robinson
3/13/2009 08:35:07 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-383

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

Attention: Ting Chen, MS
Director, Drug Regulatory Affairs

Dear Ms. Chen:

Please refer to your new drug application (NDA) date December 15, 2008, received December 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Arcapta (b) (4) (proposed) (indacaterol maleate inhalation powder, QAB149). We also refer to your submissions dated, December 19, 2008 and January 15, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is October 18, 2009

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 14, 2009.

During our filing review of your application, we identified the following potential review issues:

Clinical:

1. After preliminary assessment of the dose-ranging and dosing interval data submitted it is unclear whether the appropriate dose and dosing interval of indacaterol for the treatment of bronchospasm associated with chronic obstructive lung disease have been chosen.

2. We are concerned that the name "Arcapta [redacted] (b) (4) [redacted].

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

Clinical:

1. Submit summary dose response and dosing frequency data for indacaterol that you have collected from studies conducted to support its clinical development for patients with asthma. Include trough FEV_1, 12 and 24 hour FEV_1 time curves, data on once and twice daily dosing of indacaterol (if assessed), and data for active comparators that were given concurrently in clinical trials.

Clinical Pharmacology:

2. Submit information on the potential of indacaterol/major metabolites to induce the major CYP P450 enzymes.

3. Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PK Parameters, and other relevant study information for the following PK studies:

   a. CQAB149A2106, CQAB149A2311, CQAB149B2216, CQAB149B2220, CQAB149A2215, CQAB149B2202, CQAB149A2211, CQAB149A2221, CQAB149B2201, CQAB149A2307, CQAB149B2103, CQAB149A2212

4. Submit SAS transport files, containing ID, TRT, DOSE, individual CONC, TIME, individual PD Parameters, and other relevant study information for the following PD studies:

   a. CQAB149B2202, CQAB149B2201, CQAB149B2217

Chemistry, Manufacturing and Controls:

5. Provide a reference to 21CFR regulations for food contact materials or results from suitability tests for the [redacted] (b) (4) used to store the drug substance.

6. Provide 100% size mock ups of carton and container label.

7. Provide samples of the drug product.

8. Update the drug substance specification to include a test for [redacted] (b) (4).

9. We note that the capsule sizes for the approved Foradil Aerolizer and your proposed Arcapta [redacted] (b) (4) are the same. Provide available in vitro performance data for the indacaterol capsules being delivered by the Aerolizer device and formoterol capsule delivered by the [redacted] (b) (4) device to see if interchanging the devices and capsules provides comparable in vitro performance results. Address the possibility that patients might interchange the devices and capsules since the capsule sizes are identical and could potentially be interchanged.

10. Provide available stability and in vitro performance information for your drug product when the capsules are stored outside of the blister (as is usual for patients to put them in pill boxes) for a period of seven days.

11. Provide certifications from the excipient manufacturers that their products conform to USP OVI limits.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

Badrul Chowdhury
2/27/2009 03:48:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Office of Surveillance and Epidemiology

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Carol Hill, Project Manager, 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/16/09		22-383	N	December 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
indacaterol maleate	Standard	LABA	May 8, 2009

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
This is a request for review of the REMS which may be obtained from the EDR in the submission dated, December 15, 2008.

Mid-Cycle Review: May 12, 2009
Wrap Up: August 18, 2009
Division Goal: October 16, 2009
PDUFA Date: October 18, 2009

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER
Sean Bradley

PRINTED NAME AND SIGNATURE OF DELIVERER
Carol Hill

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
1/16/2009 11:05:47 PM
```

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Office of Surveillance and Epidemiology

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Carol Hill, Project Manager, 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/16/09		22-383	N	December 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
indacaterol maleate	Standard	LABA	July 31, 2009

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
This is a request for review of the label (proposed Trade name Arcapta [redacted] (b) (4)). The draft package insert, medication guide and carton and container labels may be found in the EDR submission dated, December 18, 2008 and January 15, 2009.
Mid-Cycle Review: May 12, 2009
Labeling Meeting: August 11, 2009
Division Goal Date: October 16, 2009
PDUFA Date: October 18, 2009

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER
Sean Bradley

PRINTED NAME AND SIGNATURE OF DELIVERER
Carol Hill

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
1/16/2009 10:58:11 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Division of Drug, Marketing, Advertising and Communications (DDMAC) WO 22 RM 1400

FROM (*Name, Office/Division, and Phone Number of Requestor*):
Carol Hill, Project Manager, 301-796-1226
Division of Pulmonary and Allergy Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/16/09		22-383	N	December 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
indacaterol maleate	Standard	LABA	July 31, 2009

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
This request is for review of the label (proposed trade name Arcapta [redacted] (b) (4)). The draft package insert, medication guide and carton and container labels may be found in the EDR submission dated, December 15, 2009 and January 15, 2009.
Mid-Cycle Review: May 12, 2009
Labeling Meeting: August 11, 2009
Division Goal Date: October 16, 2009
PDUFA Date: October 18, 2009

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER
Wayne Amchin

PRINTED NAME AND SIGNATURE OF DELIVERER
Carol Hill

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
1/16/2009 10:49:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION				REQUEST FOR CONSULTATION
TO: *(Division/Office)* Tim Robison, Ph.D., Acting Pharm/Tox Team Leader			FROM: Craig M. Bertha, Ph.D., ONDQA, Div I	
DATE 15-JAN-2009	IND NO. IND 48,649	NDA NO. N22-383	TYPE OF DOCUMENT Original NDA [505(b)(1)]	DATES OF DOCUMENTS 17-DEC-2008
NAME OF DRUG Arcapta (b) (4) (indacaterol maleate) inhalation powder		PRIORITY CONSIDERATION 1	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE by 15-MAR-2008 if possible
NAME OF FIRM: Novartis Pharmaceuticals Corporation				

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL PROGRESS REPORT NEW CORRESPONDENCE DRUG ADVERTISING ADVERSE REACTION REPORT MANUFACTURING CHANGE/ADDITION MEETING PLANNED BY	PRE-NDA MEETING END OF PHASE II MEETING RESUBMISSION SAFETY/EFFICACY PAPER NDA CONTROL SUPPLEMENT	RESPONSE TO DEFICIENCY LETTER FINAL PRINTED LABELING LABELING REVISION ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW X OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW END OF PHASE II MEETING CONTROLLED STUDIES PROTOCOL REVIEW OTHER	CHEMISTRY PHARMACOLOGY BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

DISSOLUTION BIOAVAILABLITY STUDIES PHASE IV STUDIES	DEFICIENCY LETTER RESPONSE PROTOCOL-BIOPHARMACEUTICS *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES CASE REPORTS OF SPECIFIC REACTIONS *(List below)* COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY SUMMARY OF ADVERSE EXPERIENCE POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL
COMMENTS/SPECIAL INSTRUCTIONS: Please see attached. cc: Orig. NDA # 22-383 ONDQA/DIV I/CBertha ONDQA/DIV I/AAI-Hakim OND/DPAP/CHill OND/DPAP/TRobison OND/ONDQA/DIV I/PPeri	
SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

12 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/
----------------------
Ali Al-Hakim
1/15/2009 03:34:51 PM
```

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-383

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07963-1080

Attention: Ting Chen, M.S.
Director, Regulatory Affairs

Dear Ms. Chen:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Arcapta [redacted] (b) (4) (proposed)
QAB149 (Indacaterol Maleate Inhalation Powder)

Date of Application: December 15, 2008

Date of Receipt: December 18, 2008

Our Reference Number: NDA 22-383

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

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

Sincerely,

{See appended electronic signature page}

Carol Hill, M.S.
Regulatory Health Project Manager
Division of Pulmonary and Allergy Product
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Carol F. Hill
1/8/2009 10:41:57 AM