CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207923Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207923 SUPPL # n/a HFD # 570

Trade Name: Seebri Neohaler inhalation powder

Generic Name: glycopyrrolate

Applicant Name: Novartis Pharmaceuticals

Approval Date: October 29, 2015

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)

b) 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.

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:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

Reference ID: 3839931

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

3 years

d) 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?

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).

[redacted] (b) (4)			Withdrawn
NDA#	017558	Robinul injection (Eurohealth International Sarl)	Approved
[redacted] (b) (4)			Withdrawn
[redacted] (b) (4)			Withdrawn
NDA#	022571	Cuvposa oral solution (Merz Pharmaceuticals)	Approved
NDA#	012827	Robinul tablet (Shionogi)	Approved

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 ☐

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:

(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:

NVA237A2317, NVA237A2318

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:

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"):

NVA237A2317, NVA237A2318

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 NVA237A2317

IND #48655 YES ☒ ! NO ☐
! Explain:

Investigation #2 NVA237A2318

IND #48655 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:

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:
Christine Ford, RPh
Title: Regulatory Project Manager
Date: October 29, 2015

Thru: Sandy Barnes, CPMS
Date: October 29, 2015

Name of Office/Division Director signing form:
Badrul A. Chowdhury, MD, PhD
Title: Director, Division of Pulmonary, Allergy, and Rheumatology

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CHRISTINE H CHUNG
10/29/2015

BADRUL A CHOWDHURY
10/29/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207923 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Seebri Neohaler Established Name: glycopyrrolate Dosage Form: inhalation powder		Applicant: Novartis Pharmaceuticals Agent for Applicant (if applicable):
RPM: Christine Ford		Division: DPARP

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

Actions	
• Proposed action • User Fee Goal Date is 10/29/2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Reference ID: 3845557

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 3
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
Copies of all action letters *(including approval letter with final labeling)*	Approval 10/29/2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	7/14/15 7/13/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 9/17/15 DMEPA: ☐ None 8/24/15 DMPP/PLT (DRISK): ☐ None 10/21/15 OPDP: ☐ None 10/19/15 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	9/16/15 (completed before filing) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 9/9/2015 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	2015 – 10/26, 10/23, 10/21, 10/7, 9/18, 9/15, 8/14, 7/30, 6/1, 5/27, 5/15, 4/22, 4/10, 3/12, and 1/12
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 9/28/2011
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 7/15/2008
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 10/29/2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 10/8/2015
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
Clinical Reviews	

• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review, also see CDTL review
• Clinical review(s) *(indicate date for each review)*	2015 – 9/24 and 3/2
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	9/24/15 Clinical review, page 16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None QT-IRT 7/29/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 9/10/2015
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None 2015 – 10/15, 9/25, 3/1
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2015 – 9/24, 2/24
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☐ No separate review 10/1/15
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 2015 – 9/24, 7/7, 2/19
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ None
❖ ECAC/CAC report/memo of meeting	☐ None 5/26/2014 ECAC mtg Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 2015 – 2/3
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None Microbiology 3/10/15
Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	CMC review 10/28/15, page 167
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable 10/27/2015 Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

ELECTRONIC CORRESPONDENCE

Date: October 26, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: **NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder**
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments – Prescribing Information

Total no. of pages including cover: **35**

Comments: ***Response requested no later than October 27, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

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) 796-3420. Thank you.

We refer to NDA 207923 for Seebri Neohaler and NDA 207930 for Utibron Neohaler. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

For Section 14.2 Confirmatory Trials:

> We have reviewed your comments and proposed language regarding secondary endpoints. We have also reviewed the approved package inserts for similar drugs. Based on your comments, and our review, we have amended our language in the Utibron Neohaler package insert to be consistent with what is in the package insert of other approved drugs of the class (i.e., Anoro Ellipta). While it appears that we do not have prior precedence for inclusion of this language in the Seebri Neohaler (a single ingredient LAMA) package insert, we have included the language in the Seebri package insert for your consideration. The information we have included provides information to providers regarding how much improvement one can expect in peak FEV1 on Day 1 as compared to the end of study, in this case Day 85, after chronic dosing. Our proposed language also includes re-insertion of the onset of action language that was previously deleted. Note that we are using the definition of onset of action as pre-specified in your protocol. The language proposed by the Agency was arrived at after extensive internal discussion and deliberation; therefore, while you may propose minor changes/corrections to our labeling language, substantial changes will not be entertained at this time.

FDA edits were made as tracked changes to your proposed labeling emailed October 23, 2015, with official submission planned for October 26, 2015. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov no later than October 27, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: review team in shrepoint/ 10.26.2015
cford/ 10.26.2015

Thru: BKarimi-Shah/ 10.26.2015

Initialed by: SBarnes/ 10.26.2015

Finalized: cford/ 10.26.2015

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

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

/s/

CHRISTINE H CHUNG
10/26/2015
Christine Ford (formerly Chung)

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

ELECTRONIC CORRESPONDENCE

Date: October 23, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: **NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder**
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments – Patient labeling

Total no. of pages including cover: **22**

Comments: ***Response requested no later than October 27, 2015***

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We refer to NDA 207923 for Seebri Neohaler and NDA 207930 for Utibron Neohaler. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

FDA edits were made as tracked changes to your proposed labeling submitted October 15, 2015. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov no later than October 27, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: DMPP-OPDP/ 10.21.2015
cford/ 10.23.2015

Thru: BKarimi-Shah/ 10.23.2015

Initialed by: SBarnes/ 10.23.2015

Finalized: cford/ 10.23.2015

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/s/

CHRISTINE H CHUNG
10/23/2015
Christine Ford (formerly Chung)

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

ELECTRONIC CORRESPONDENCE

Date: October 21, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: **NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder**
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments

Total no. of pages including cover: **40**

Comments: ***Response requested no later than October 23, 2015***

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Document to be mailed: YES ☑ NO

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We refer to NDA 207923 for Seebri Neohaler, NDA 207930 for Utibron Neohaler, and to your submission dated October 15, 2015. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

A. For both NDAs 207923 and 207930

1. Regarding Novartis Comment 3 (Section 2.3), we appreciate your correction and proposal to use the human systemic exposure (AUC0-24h) of 0.221 base ng.h/mL derived from study CQVA149A2107. Further, we agree with your dose ratios, using the base values for systemic exposure (AUC) for both the clinical and nonclinical studies. As you stated, there were no appreciable differences in dose ratios using either the base or salt form.

2. Regarding Novartis Comment 4 (Section 2.4), we again appreciate your correction and proposal to use the human systemic exposure (AUC0-24h) of 1.030 base ng.h/mL derived from study CQVA149A2107. Further, we agree with your proposed dose ratios.

3. We have considered your comments under Novartis Comment 5 (Section 2.5), but do not agree with your entire assessment. (b) (4)

   In the case of glycopyrrolate, the combined eye findings in the rat and dog are a concern, and we consider them to be consistent with the mechanism of action of glycopyrrolate. Data and statements in your study reports clearly support that eye findings are test article related in both rats and dogs. Regarding the findings in the 39-week dog study, we agree with your assessment that the focal nuclear opacities may be incidental, (b) (4)
   The eye findings of bilateral and unilateral lenticular changes (anterior capsular opacity, anterior prominent suture line, anterior slight cataract) in the rat, and conjunctivitis and corneal opacity in the dog remain as test article related findings in our proposed labeling. We have adjusted the dose ratios using the base form AUC0-24hr for animal data, and the corrected clinical AUC0-24hr value for glycopyrrolate, as shown in the table below. To simplify the labeling text, we have eliminated (b) (4) and stated the lower dose ratio between the sexes in rats and in dogs.

		Nonclinical dose corresponding to eye finding		Dose ratio for clinical dose of 31.2 mcg NVA237
Study	Sex	Achieved dose (mg/kg/day, salt form)	AUC (ng*hr/mL) (base form)	AUC = 0.221 ng*hr/mL (base form)
26 week rat	Both	4.98	334	1500
	Both	0.67	61.6	280
	Both	0.09	13.8	60
39 week dog	Male	0.33	80.9	370
	Female		32.8	150
	Male	0.12	21.3	100
	Female		33.6	150

Dose ratios are rounded

B. Only for NDA 207930 Utibron

1. Section 14.1 Dose Ranging Trials

   We do not agree with your proposal/rationale to delete the [redacted] information from this section. The example your provide with respect to [redacted] is not relevant; [redacted] We refer you to the package insert of [redacted] for a more typical example. For this reason, we have re-inserted the [redacted] information back into this section.

2. Section 14.2 Confirmatory Trials

   - We acknowledge your removal of the table listing the secondary endpoints and reformatting into a narrative format. However, reporting the secondary endpoints with this degree of granularity is unnecessary. We have re-inserted the prior language describing that the results were significant for these parameters, without reporting the numbers.
   - The [redacted] is not appropriate for labeling claims, [redacted] We have removed this statement.
   - With respect to the SGRQ, we note your reference to Jones et. al.[1] Based on our review of this article, we disagree with your conclusion that [redacted]

[1] Jones PW et al. Minimal Clinically Important Differences in Pharmacological Trials. Am J Respir Crit Care Med 2014; 189: 250 - 255.

(b) (4)

When evaluating a combination therapy in which one of the monocomponents has already shown a benefit over placebo, the most important comparison is not of the combination to placebo (as one would expect this comparison to be positive even in the setting that the second component contributes nothing), but of the combination to each component. In order to evaluate the benefit of the combination over each single entity, the authors advocate for a responder analysis and propose the term "minimum worthwhile incremental advantage" to describe the percentage of patients who would experience improvement at or above the MCID on adding one treatment to another, or comparing two active treatments. As the "minimum worthwhile incremental advantage" is not defined, the best way to communicate this information to providers is to provide information regarding the relevant pairwise comparisons between the combination product, monoproducts, and placebo. Therefore, we have described the results in more detail for the trial which demonstrated statistically significant pairwise comparisons, reporting both responder rates and odds ratios, and provided only odds ratios for the trial which trended in favor of "incremental benefit" of the combination over the monotherapies, without showing a statistically significant difference. This language communicates the data in a neutral matter without favoring one set of pairwise comparisons over another. We prefer reporting the SGRQ results of both trials, as we have done in the attached label, giving more detailed information for Trial 2. We discourage any labeling modification that proposes removal of Trial 1 results, as this will result in a change in our position as to which trial should be reported in detail in labeling. While you may propose minor modifications to our language, we discourage major changes to the SGRQ labeling language.

FDA edits were made as tracked changes to your proposed labeling submitted October 15, 2015. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by close of business (COB) October 23, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison/ 10.21.2015
BKarimi-Shah/ 10.21.2015
cford/ 10.21.2015

Initialed by: SBarnes/ 10.21.2015

Finalized: cford/ 10.21.2015

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CHRISTINE H CHUNG
10/21/2015

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

ELECTRONIC CORRESPONDENCE

Date: October 7, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: **NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder**
NDA 207930 Utibron Neohaler (glycopyrrolate/indacaterol) Inhalation Powder
FDA labeling comments

Total no. of pages including cover: **67**

Comments: ***Response requested no later than October 15, 2015***

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We refer to NDA 207923 for Seebri Neohaler, NDA 207930 for Utibron Neohaler, and to your submission dated September 22, 2015. We have the following labeling comments. Additional labeling changes may be forthcoming as we continue to review the labeling.

1. We have reviewed your response dated September 22, 2015, and have the following comment to your response to Question 2, regarding study 0870596 entitled, "A subcutaneous fertility and early embryonic development study in rats", as it applies to Section 13.1 of the proposed labeling language for glycopyrrolate. We agree with your application of the historical control data for the number of corpora lutea, implantation sites, live fetuses and pre-implantation losses at the mid-dose of 0.5 mg/kg/day. Thus, we agree that there appears to be no test article related effect on fertility and reproductive potential based on these parameters at the mid-dose of 0.5 mg/kg/day. However, the historical data did not cover these parameters at the high-dose of 1.5 mg/kg/day indicating adverse drug-related effects at this dose. We cannot agree that (b) (4) Thus, we have included language in the proposed labeling that states fertility was adversely affected at the dose of 1.5 mg/kg/day of glycopyrrolate in both males and females. To be consistent with the proposed dose of 15.6 mcg of glycopyrrolate (salt form), all nonclinical doses of glycopyrrolate have been represented in the label in the salt form. Therefore, in the case of the rat fertility data, we propose to use the dose of 1.88 mg/kg/day (salt form), which corresponds to 1.5 mg/kg/day (base form).

2. Regarding labeling for both NDA 207923 and 207930, we have listed all doses for nonclinical studies in the salt form for glycopyrrolate, and in the base form for indacaterol.

3. In calculating the dose ratios for glycopyrrolate, we have utilized the human systemic exposure (AUC) of 0.139 ng.h/mL (salt form), derived from study # CQVA149A2107 (0.111 ng*h/mL, base form), corresponding to the proposed dose of 31.2 mcg glycopyrrolate (salt form). The following table illustrates the how dose ratios were calculated for the nonclinical sections covering carcinogenicity, and reproductive and developmental effects.

Study	Route	Sex	Dose (mg/kg; salt)	AUC (ng.h/mL; salt)	Dose Ratio Clinical AUC = 0.139 (ng.h/mL; salt)	Rounded Clinical AUC = 0.139 (ng.h/mL; salt)	
Carcinogenesis							Study #
2 year rat	IH	Both	0.56	45.6	328.1	330	r670435
Reproductive and Development							
Fertility in rats	SC	Male	1.88	519	3733.8	3700	r870596
Fertility in rats	SC	Female	1.88	290	2086.3	2100	r870596
Fertility in rats	SC	Both	0.63	98.0	705.0	710	r870596
EFD in rats	IH	Female	3.83	388	2791.4	2800	r680006
EFD in rabbits	IH	Female	4.4	148	1064.7	1100	r870597
PPND in rats	SC	Female	1.88	290	2086.3	2100	r870598*

*AUC value extrapolated from study r870596.

4. In calculating the dose ratios for indacaterol, we have utilized the human systemic exposure (AUC) of 0.515 ng.h/mL (base form), derived from study # CQVA149A2107, (b) (4) . The following table illustrates the how dose ratios were calculated for the nonclinical sections covering carcinogenicity, and reproductive and developmental effects.

Study	Route	Sex	Dose (mg/kg; base)	AUC (ng.h/mL; base)	Dose Ratio Clinical AUC = 0.515 (ng.h/mL; base)	Rounded Clinical AUC = 0.515 (ng.h/mL; base)	
Carcinogenesis							Study #
2 year rat	IH	Both	2.09	116	225.2	230	320002
Reproductive and Development							
Fertility in rats	SC	Male	2.0	921	1788.3	1800	270074
Fertility in rats	SC	Female	2.0	694	1347.6	1300	270074
EFD in rats	SC	Female	1.0	345	669.9	670	270037
EFD in rabbits	SC	Female	1.0	795	1543.7	1500	270038
PPND in rats	SC	Female	0.3	114	221.4	220	270185*

*AUC value extrapolated from study 0270037.

5. Eye findings were identified in the pivotal chronic toxicology studies with NVA237 in rats and dogs. In the 26 week inhalation toxicology study (Study # r0580297/79031), rats received estimated achieved doses of 0 (air), 0 (vehicle: 1% magnesium stearate, 99% lactose monohydrate), 0.09, 0.67 and 4.98 mg/kg of NVA237 (salt form). Eye findings consisted of bilateral and unilateral lenticular changes (anterior capsular opacity, anterior prominent suture line, anterior slight cataract) that were observed at doses of 0.67 mg/kg and above (approximately 440 times and above the MRHD in adults on an AUC basis.) These findings were partially reversible.

   In the 39 week inhalation toxicology study (Study #r0670548), beagle dogs were dosed with 0 (air), 0 (vehicle: 1% magnesium stearate, 99% lactose monohydrate),

0.030, 0.12, and 0.33 mg/kg (estimated achieved doses in salt form) through the inhalation route of exposure. Test article related ophthalmic findings were bilateral conjunctival hyperemia, corneal opacity, and focal nuclear opacity observed at 0.33 mg/kg (in male and female dogs at approximately 770 and 290 times the MRHD in adults on an AUC basis, respectively). These findings were reversible.

Regarding eye findings listed under Section 13.2 of both labels under NDAs 207923 and 207930, we calculated the dose ratios based on the following systemic exposures (AUCs):

		Nonclinical dose corresponding to eye finding		Dose ratio for clinical dose of 31.2 mcg NVA237
Study	Sex	Achieved dose (mg/kg/day, salt form)	AUC (ng*hr/mL) (salt form)	AUC = 0.139 ng*hr/mL (salt form)
26 week rat	Both	4.98	334	2400
	Both	0.67	61.6	440
	Both	0.09	13.8	100
39 week dog	Male	0.33	101.2	730
	Female		41.0	290
	Male	0.12	26.6	190
	Female		42.0	300

FDA edits were made as tracked changes to your proposed labeling submitted December 29, 2014. Any additional proposed changes you may have can be made in a similar fashion by using the clean Word version of the attached labeling and edit using tracked changes.

Submit revised draft labeling incorporating the requested changes to me via secure email at christine.ford@fda.hhs.gov by close of business (COB) October 14, 2015. Your response will subsequently need to be submitted officially to the NDA.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: cford/ 10.6.2015

Initialed by: SBarnes/ 10.7.2015
JSohn, TRobison/ 10.7.2015
ETorjusen, BKarimi-Shah/ 10.7.2015

Finalized: cford/ 10.7.2015

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/s/

CHRISTINE H CHUNG
10/07/2015
Christine Ford (formerly last name Chung)

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

ELECTRONIC CORRESPONDENCE

Date: September 18, 2015

To: Bisola Ashiru Filchak, MPH Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: **NDA 207923 Seebri Neohaler (glycopyrrolate) inhalation powder**
NDA 207930 Utibron (indacaterol/glycopyrrolate) inhalation powder
FDA request for information – Nonclinical

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

Comments: ***Information requested no later than September 22, 2015***

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Document to be mailed: YES ☑ NO

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder are currently under review, and we have the following request for information:

1. In proposed labeling for Utibron Neohaler, Section 8.3 states that "Indacaterol (including its metabolites) have been detected in the milk of lactating rats." The Nonclinical Overview for NDA 207930 includes the following statement, "Indacaterol and/or its metabolites passed the placenta-blood-barrier in pregnant rats and were transferred rapidly into the milk of lactating rats (Study R02-0220) (Study R0700884)."

   Provide the location of the study report(s) for R02-0220 and R0700884 in NDA 207930.

2. For study 0870596 entitled, "A subcutaneous fertility and early embryonic development study in rats," the study report concluded that there were no test article related effects on fertility. Rats received subcutaneous (SC) doses of 0 (vehicle, 5% dextrose), 0.19, 0.63, 1.88 mg/kg/day (salt) to assess fertility.

   You noted that the fertility index was generally low in all groups, including the control (control 72%, LD 60%, MD 84%, HD 60%). This effect was not dose dependent. You also noted that studies conducted "recently" in the same facility had fertility rates that ranged from 84% to 96%, and that only the MD had a fertility rate within the expected range. There is a concern that the cause of the decreased fertility rate may mask a test article related effect.

   Further, at the MD and HD, there was a slight decrease in the litter mean number of corpora lutea (control 13.2, LD 13.6, MD 12.6, HD 11.0) and number of implantations (control 11.6, LD 12.3, MD 9.9, HD 7.9), which corresponded to a decreased number of live fetuses per litter (control 10.9, LD 11.6, MD 9.9, HD 7.9). The decrease in implantations and live fetuses at the MD and HD may be a result of increased preimplantation loss at the MD and HD (control 12.1%, LD 9.9%, MD 19.8%, HD 22.4%), compared to the control and LD. Based on these dose dependent trends, it is difficult to rule out an effect of the test article on these parameters.

   It appears reasonable to conclude that fertility may have been adversely affected by the test article at the MD and HD, which are associated with decreased number of corpora lutea, implantations, and live fetuses, and increased preimplantation loss. Fertility does not appear to have been adversely effected at the LD of 0.19 mg/kg NVA237 (salt).

   Provide further justification for your interpretation of a lack of test article related adverse findings in fertility parameters at the MD and HD.

Submit the requested information as official responses to the NDAs no later than September 22, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison/ 9.17.2015
cford/ 9.17.2015

Initialed by: SBarnes/ 9.18.2015
JSohn, TRobison/ 9.18.2015

Finalized: cford/ 9.18.2015

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CHRISTINE H CHUNG
09/18/2015

Food and Drug Administration
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ELECTRONIC CORRESPONDENCE

Date: September 15, 2015

To: Bisola Ashiru Filchak, MPH Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: **NDA 207923 Seebri Neohaler (glycopyrrolate) inhalation powder**
NDA 207930 Utibron (indacaterol/glycopyrrolate) inhalation powder
FDA request for information – Nonclinical

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

Comments: ***Information requested no later than September 21, 2015***

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Utibron Neohaler (indacaterol/glycopyrrolate) inhalation powder are currently under review, and we have the following request for information:

In the 39 week dog study (study #79334/0670548), ophthalmic findings were identified by a board certified ophthalmologist:

> "…mucoid ocular discharge, conjunctival hyperemia, faint corneal opacities, evidence of previous corneal ulceration and in one animal of receiving 0.33/0.27 mg/kg/day, slight unilateral diffuse corneal edema accompanied by aqueous flare and superficial corneal vascularization. Findings were uni- or bilateral, mostly intermittent and mild, and no longer observed at the time of recovery"

The study report provides individual ophthalmological data for the findings mentioned above (pages 954 - 959), but no summary tables for these findings were provided. Provide a summary table indicating unilateral or bilateral eye findings to assist in our interpretation of the data. The study report should be subsequently amended to include this information.

Submit the requested information as official responses to the NDAs no later than September 21, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison/ 9.15.2015
cford/ 9.15.2015

Initialed by: SBarnes/ 9.15.2015

Finalized: cford/ 9.15.2015

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CHRISTINE H CHUNG
09/15/2015

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

ELECTRONIC CORRESPONDENCE

Date: August 14, 2015

To: Bisola Ashiru Filchak, MPH Jennifer Evans, PharmD Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159 862-778-6061	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com jennifer.evans@novartis.com	**Phone number:** 301-796-3420

Subject: **NDA 207923 Seebri Neohaler (glycopyrrolate) capsules for inhalation**
NDA 207930 Utibron (indacaterol/glycopyrrolate) capsules for inhalation
FDA request for information – Statistics

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

Comments: ***Information requested no later than August 21, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Ubitron Neohaler (indacaterol/glycopyrrolate) capsules for inhalation are currently under review, and we have the following requests for information:

Provide tipping point sensitivity analyses to evaluate the impact of missing data for the primary endpoint in trials NVA237A2317, NVA237A2318, QVA149A2336, and QVA149A2337. These analyses should vary assumptions about average values of the relevant endpoint among the patients on NVA237, QVA149, QAB149 and placebo arms who withdrew from the trial early. Include the possibility that patients with missing data from the active arms had worse outcomes than patients with missing data from the placebo arm. Ensure that documentation submitted with your report defines the distributions used to generate values for withdrawn patients and explains how those distributions were obtained.

Provide the datasets and programs for all analyses. The analysis datasets should include a column or columns which clearly indicate whether each observation was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

Submit the requested information as official responses to the NDAs no later than close of business (COB) August 21, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: KHamilton, DPetullo/ 8.13.2015
cford/ 8.13.2015

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CHRISTINE H CHUNG
08/14/2015

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ELECTRONIC CORRESPONDENCE

Date: July 30, 2015

To: Bisola Ashiru Filchak, MPH Jennifer Evans, PharmD Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159 862-778-6061	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com jennifer.evans@novartis.com	**Phone number:** 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Capsules for Inhalation
NDA 207930 Utibron (indacaterol/glycopyrrolate) Capsules for Inhalation
FDA request for information – Nonclinical and CMC

Total no. of pages including cover: **4**

Comments: ***Information requested no later than August 12, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

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NDA 207923 for Seebri Neohaler (glycopyrrolate) and NDA 207930 for Ubitron Neohaler (indacaterol/glycopyrrolate) Capsules for Inhalation are currently under review, and we have the following requests for information:

1. We note that your proposed acceptance criteria for degradants (b) (4) differ between NDA 207923 and NDA 207930. In NDA 207923, you propose a specification of NMT (b) (4)% for (b) (4) and NMT (b) (4)% for (b) (4). In NDA 207930, you propose a specification of NMT (b) (4)% for (b) (4) and NMT (b) (4)% for (b) (4).

   Degradants exceeding (b) (4)% should be qualified by safety data from a 13-week animal study to support chronic use for maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis.

   We note that the justification for the acceptance criteria of NMT (b) (4)% for (b) (4) and NMT (b) (4)% for (b) (4) is limited to data from your submitted 4-week Rat Study with Degradation Products (study #0870163), Mutagenicity Test Using Salmonella (study #0870161), and Induction of Chromosome Aberrations in Peripheral Blood Lymphocytes (study #0870162).

   In order to address this issue you may either:

   a. Amend the specification to limit the acceptance criteria of (b) (4) and (b) (4) to NMT (b) (4)% for each degradant in NDA 207923.

      OR

   b. Submit a 13-week rat study with safety data or submit additional justification to support the proposed acceptance criteria of NMT (b) (4)% for (b) (4) and NMT (b) (4)% for (b) (4) under NDA 207923.

2. We have the following questions regarding your Inhalation Embryo Fetal Development Study in Rats (study #900863/ 0680006). We refer to your following schedule from page 23 of your study report which states that the first day of treatment was on December 4, 2006 (which we interpret as corresponding to Gestation Day 6 for some animals) and the last treatment was on December 20, 2006 (which we interpret as corresponding to Gestation Day 17 for some animals).

Major activities	Date
Protocol signed	22-Nov-2006
Animal arrival	22-Nov-2006
Placement for mating	27-Nov-2006
Start of acclimatization/pretest/randomization	01-Dec-2006
Date of first treatment	04- Dec-2006
Date of last treatment	20- Dec-2006
Date of last cesarean	24- Dec-2006

a. On page 118, the filter concentrations pre-study (Nov 24, 2006) for groups 4, 5, 6 appear to be positive for the NVA237. Confirm that these filter concentrations were obtained from testing of the chambers without animals present on November 24, 2006, prior to the dosing of animals with NVA237.

b. On pages 36-48, summary tables provided concentrations of NVA 237 from homogeneity data, and from chamber concentrations. Clarify the labels used for the tables. For example, on page 36, the first sample concentration is given for "sample position TA1". Further, on page 39, the first sample concentration is given for "Rep 1".

3. We have the following questions regarding your Inhalation Embryo Fetal Development Study in Rabbits (study #901910/0870597). We refer to your following schedule from page 23 of your study report which states that the first day of treatment was on April 20, 2009, and the last treatment was on May 5, 2009.

Major activities	Date
Protocol signed	15-Apr-2009
Animal arrival/start of acclimatization/pretest	15 and 17-Apr-2009
Animal randomization	18 to 21-Apr-2009
Date of first treatment	20-Apr-2009
Date of last treatment	05-May-2009
Date of last cesarean	15-May-2009

a. On page 112, the pre-study (Apr 3, 2009) data for groups 2, 3, and 4 appear to be positive for the NVA237. Confirm that these filter concentrations were obtained from testing of the chambers without animals present on April 3, 2009, prior to the dosing of animals with NVA237.

b. On pages 40-54, summary tables provided the concentrations of NVA 237 from homogeneity data, and from chamber concentrations. Clarify the labels used for the tables. For example, on page 40, the first sample concentration is given for "sample position GA1". Further, on page 43, the first sample concentration is given for "Rep 1 7".

Submit the requested information as official responses to the NDAs no later than close of business (COB) August 12, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison, AShaw, CBertha/ 7.30.2015
cford/ 7.30.2015

Initialed by: SBarnes/ 7.30.2015

Finalized: cford/ 7.30.2015

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/s/

CHRISTINE H CHUNG
07/30/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207923

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novartis Pharmaceuticals Corporation
One Health Plaza
Building 100
East Hanover, New Jersey 07936-1080

ATTENTION: Bisola Ashiru Filchak, MPH
Director, Drug Regulatory Affairs

Dear Ms. Filchak:

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Glycopyrrolate Capsules for Inhalation, 15.6 mcg.

We also refer to your correspondence dated and received April 24, 2015, requesting review of your proposed proprietary name, Seebri Neohaler.

We have completed our review of the proposed proprietary name, Seebri Neohaler and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 24, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

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 Christine Ford, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
07/14/2015

Ford, Christine

From: Ford, Christine
Sent: Monday, June 01, 2015 12:50 PM
To: Ashiru, Bisola
Cc: Ford, Christine
Subject: Request for information: NDA 207923 Seebri Neohaler

Dear Bisola,
We refer to NDA 207923 for Seebri Neohaler (glycopyrrolate). Regarding the QT study report, we have the following request for information.
Although we were able to locate the PK concentration dataset, submit the following so that we may continue to review your application:

1. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses.
2. The ECG raw data set should include at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g., QTcB, QTcF, QTcI - if there is a specifically calculated adjusting/slope factor, also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).

Submit the requested information as an official response to the NDA no later than close of business June 4, 2015, or provide a timeline for when the information will be submitted.
Please contact me if you have any questions. Thanks.
Christine

Christine Ford, RPh
CDR, USPHS
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
FDA/CDER/OND/ODE II
Phone 301-796-3420
Fax 301-796-9728
christine.ford@fda.hhs.gov

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/s/

CHRISTINE H CHUNG
06/01/2015

Executive CAC
Date of Meeting: May 26, 2015

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Timothy McGovern, Ph.D., OND IO, Member
Jane J. Sohn, Ph.D., DPARP, Presenting Reviewer (Acting Pharm Tox Supervisor)

Author of Minutes: Jane J. Sohn, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 207923, 207930
Drug Name: Glycopyrronium bromide (GP), GP/Indacaterol
Sponsor: Novartis

Novartis submitted results from a 2-year inhalation carcinogenicity study in rats and a 26-week oral carcinogenicity study in transgenic mice administered GP. The doses used in the studies were recommended by the Committee (see minutes dated 10/5/2006 (rat) and 2/24/10 (mouse) under IND 48655). Carcinogenicity studies with indacaterol alone were previously reviewed under NDA 22383.

Glycopyrronium bromide was negative in genetic toxicology testing based on results from the *in vitro* bacterial reverse mutation, human peripheral lymphocyte chromosomal aberration assay, and the *in vivo* rat micronucleus assay.

Rat Carcinogenicity Study
In a 2-year bioassay in Wistar rats (50 animals/sex/group), animals received GP by inhalation (nose-only) at doses of 0 (air, on loading rack in restraint tubes in separate room), 0 (air, rotated on a flow through chamber), 0 (vehicle: 1% magnesium stearate and 99% lactose monohydrate), 0.06, 0.17, 0.45 mg/kg/day GP through 60-minute exposures (estimated achieved doses, quaternary ammonium cation of the bromide salt). The first air control group (Air1) showed increased body weight compared to all other groups, and was not used for analysis. Statistical analyses were done against the vehicle control and second air control (Air2) groups.

No statistically significant neoplastic findings were observed in male or female rats. GP was associated with decreased body weight in males at all doses, and in HD females. NVA 237 had no effect on mortality. Systemic exposure (AUC) to GP was similar in both genders, and slight accumulation was observed at Week 52. Exposure was dose proportional between the LD and MD, but was slightly less than dose proportional between the MD and HD. Systemic exposures (AUC) at the HD exceeded the maximum anticipated clinical exposure in COPD patients by more than 300-fold.

Tg.rasH2 Mouse Carcinogenicity Study
In a 26-week bioassay, Tg.rasH2 mice (25/sex/group) received GP by oral gavage at 0 (vehicle: Deionized water), 10, 25, and 75 mg/kg/day in males, and 0 (vehicle), 10, 30, and 100 mg/kg/day in females. Positive control mice were administered N-methyl-N-nitrosourea (MNU; 75 mg/kg) by a single intraperitoneal injection on Day 1.

No statistically significant neoplastic findings were observed in male or female Tg.rasH2 mice. GP was associated with decreased body weight in male and female Tg.rasH2. NVA 237 had no effect on mortality in Tg.rasH2 mice. Due to inconsistent exposure to GP, exposure to the metabolite CJL603 was measured. Systemic exposure (AUC) for CJL603 was detected in at least 2 of 3 HD male and female Tg.rasH2 mice at 0.5, 1, 3, and 7 hrs post dose. Based on limited data for CJL603, AUC increased in a roughly dose proportional manner.

As expected, MNU-treated Tg.rasH2 animals had increased mortality and neoplasia incidence, compared to control Tg.rasH2 animals.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in either male or female rats.

Mouse:

- The Committee found that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in either male or female Tg.rasH2 mice.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, DPARP
/Timothy Robison, DPARP
/Jane Sohn, DPARP
/Carol Galvis, DPARP
/Christine Ford, DPARP
/ASeifried, OND IO

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/s/

JANE J SOHN
05/28/2015

ABIGAIL C JACOBS
05/28/2015

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

ELECTRONIC CORRESPONDENCE

Date: May 27, 2015

To: Bisola Ashiru Filchak, MPH Jennifer Evans, PharmD Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159 862-778-6061	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com jennifer.evans@novartis.com	**Phone number:** 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules
NDA 207930 indacaterol/glycopyrrolate Inhalation Powder Hard Capsules
FDA request for information – Clinical / Office of Scientific Investigations

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

Comments: ***Information requested no later than June 3, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

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NDAs 207923 and 207930 for glycopyrrolate and indacaterol/glycopyrrolate Neohaler Inhalation Powder Hard Capsules are currently under review, and we have the following request for information:

- During the FDA site inspection of Dr. Pearle for Study NVA237A2317, the inspectors noted that randomization numbers were not available at the study site; only kit numbers were provided. Clarify how the randomization number corresponds to the kit number. Include other study protocols NVA237A2318, QVA149A2336, QVA149A2337, if applicable.
- The raw spirometry data provided at the study site for study NVA237A2317 (Dr. Pearle) does not correspond with the adjusted data submitted to the NDA. Submit clarification about how the raw spirometry data was adjusted in the NDA. Include other study protocols NVA237A2318, QVA149A2336, QVA149A2337, if applicable.

Submit the requested information as official responses to the NDAs no later than close of business (COB) June 3, 2015. If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: ETorjusen, BKarimi-Shah, AOrencia/ 5.26.2015
cford/ 5.27.2015

Initialed by: SBarnes/ 5.27.2015

Finalized: cford/ 5.27.2015

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/s/

CHRISTINE H CHUNG
05/27/2015

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

ELECTRONIC CORRESPONDENCE

Date: May 15, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules
FDA request for information – Nonclinical

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

Comments: ***Information requested by no later than May 20, 2015***

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NDA 207923 for Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules is currently under review, and we have the following request for information:

We have questions regarding the survival incidences for males in Group 2 (Air 2) and females in Group 6 (0.45 mg/kg/day) from your 2-year rat carcinogenicity study (study #0670435/79032).

On page 46, you provided the following survival data:

Table 4-4 Survival at week 104 is summarized below

Group Number/ Sex	Dose (mg/kg/day)	Survival	
		S	%
1/ Males	0	35/50	70
1/ Females	0	29/50	58
2/ Males	0	36/50	72
2/ Females	0	35/50	70
3/ Males	0	35/50	70
3/ Females	0	36/50	72
4/ Males	0.07	44/50	88
4/ Females	0.07	34/50	68
5/ Males	0.21	38/50	76
5/ Females	0.21	36/50	72
6/ Males	0.56	37/50	74
6/ Females	0.56	33/50	66

S Number of Survivors
% Percent of the original group size

Upon analysis of individual animal data under the Pathology Report, we found the following survival numbers as listed in the table below. Apparent inconsistencies in survival incidences were noted with reference to summary data for males in Group 2 (Air 2) and females in Group 6 (0.45 mg/kg/day):

	Males	Females
Group/Dose (mg/kg/day)	# Surviving/Total	# Surviving/Total
Air 1	35/50	29/50
Air 2	**35/50**	35/50
Vehicle	35/50	36/50
0.06	44/50	34/50
0.17	38/50	36/50
0.45	37/50	**32/50**

We have listed the following summary of individual animal data for the two groups of interest, based on the Pathology Report:

		Animal #	Status	Cause of death	Day	Dead (n)	Survived (n)
Group 2	male	2006	UE	Subcutaneous tissue: malignant schwannoma	591	-	-
		2007	UE	Subcutaneous tissue: malignant schwannoma	721		
		2008	UE	Pituitary: adenoma: pars distalis	482		
		2010	UE	Hemolymphoreticular tissue: malignant lymphoma	204		
		2011	UE	Pituitary: adenoma: pars distalis	608		
		2015	UE	Preputial gland: inflammation, chronic, grade 5	632		
		2019	UE	Pituitary: adenoma: pars distalis	596		
		2020	UE	Pancreas: carcinoma, acinar cell	680		
		2023	UE	Subcutaneous tissue: fibroma	632		
		2024	FD	Subcutaneous tissue: lipoma	476		
		2029	FD	Spleen: leiomyosarcoma	512		
		2033	FD	Pituitary: adenoma: pars distalis	688		
		2036	FD	not stated	638		
		2037	FD	Adrenal: malignant pheohromocytoma, unilat	733		
		2045	FD	not stated	687	15	35
	female	2501	UE	Uterus: adenocarcinoma: endometrial	249		
		2505	FD	Pituitary: adenoma: pars distalis	585		
		2508	UE	Pituitary: adenoma: pars distalis	468		
		2509	FD	Uterus: dilatation, grade 4	570		
		2513	UE	Undetermined	624		
		2514	UE	Mammary gland: adenomacarcioma	596		
		2516	UE	Uterus: sarcoma, endometrial stromal	554		
		2519	UE	Uterus: dilatation, grade 4	623		
		2521	UE	Pituitary: adenoma: pars distalis	525		
		2526	UE	Pituitary: adenoma: pars distalis	646		
		2527	UE	Pituitary: carcinoma: pars distalis, malignant	582		
		2533	FD	Pituitary: adenoma: pars distalis	580		
		2535	UE	Pituitary: adenoma: pars distalis	686		
		2539	UE	Uterus: adenocarcinoma: endometrial	724		
		2547	UE	Pituitary: adenoma: pars distalis	682	15	35
Group 6	male	6003	UE	Testis: adenoma, interstitial cell, unilat	496		
		6008	FD	Undetermined	87		
		6013	UE	Pituitary: adenoma: pars distalis	682		
		6015	UE	Brain: malignant astrocytoma	682		
		6026	UE	Pituitary: adenoma: pars distalis	665		
		6031	FD	Undetermined	55		
		6033	UE	Undetermined	339		
		6036	FD	Abdomen: inflammation, grade 4	651		
		6040	FD	Undetermined	521		

		Animal #	Status	Cause of death	Day	Dead (n)	Survived (n)
		6042	FD	Undetermined	615		
		6044	FD	Undetermined	725		
		6047	FD	Undetermined	376		
		6050	UE	Skin misc: sarcoma	430	13	37
	female	6507	FD	Pituitary: adenoma: pars distalis	617		
		6508	UE	Pituitary: adenoma: pars distalis	601		
		6509	FD	Uterus: adenocarcinoma, enometrial	709		
		6510	UE	Skin misc: ulceration, grade 3	636		
		6513	FD	Pituitary: adenoma: pars distalis	706		
		6519	FD	Thymus: thymoma, malignant	604		
		6524	UE	Uterus: malignant schwannoma	618		
		6525	UE	Thymus: thymoma, malignant	636		
		6529	FD	Pituitary: adenoma: pars distalis	650		
		6530	UE	Pituitary: adenoma: pars distalis	744		
		6531	FD	Undetermined	94		
		6535	UE	Pituitary: adenoma: pars distalis	695		
		6537	UE	Pituitary: adenoma: pars distalis	437		
		6538	UE	Uterus: polyp, endometrial stromal	420		
		6540	UE	Pituitary: adenoma: pars distalis	584		
		6541	UE	Uterus: cyst, grade 4	601		
		6546	FD	Mammary gland: fibroadenoma	630		
		6548	UE	Pituitary: adenoma: pars distalis	689	18	32

Provide clarification for the apparent inconsistencies of survival incidences between the summary survival data provided on page 46, and the interpretation of your individual animal data shown above from the Pathology Report.

Submit the requested information as an official response to the NDA no later than May 20, 2015, or provide a timeline for when the information will be submitted. In addition, an amended report to correct the apparent inconsistencies of survival incidences should be submitted to the NDA as necessary.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: JSohn, TRobison/ 5.13.2015
cford/ 5.15.2015

Initialed by: SBarnes/ 5.15.2015

Finalized: cford/ 5.15.2015

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CHRISTINE H CHUNG
05/15/2015

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

ELECTRONIC CORRESPONDENCE

Date: April 22, 2015

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules
FDA request for information – Clinical Pharmacology

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

Comments: ***Information requested by no later than April 26, 2015***

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Document to be mailed: YES ☑ NO

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NDA 207923 for Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules is currently under review, and we have the following request for information:

1. Provide analysis-ready datasets used for dose response analysis in Study NVA237A2208. Data should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
2. Provide corresponding model codes or control streams and output listings. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Submit the requested information as an official response to the NDA no later than April 26, 2015, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: Lei He, SDoddapaneni/ 4.20.2015
cford/ 4.21.2015

Initialed by: SBarnes/ 4.22.2015

Finalized: cford/ 4.22.2015

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/s/

CHRISTINE H CHUNG
04/22/2015

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

ELECTRONIC CORRESPONDENCE

Date: April 10, 2014

To: Bisola Ashiru Filchak, MPH Director, Drug Regulatory Affairs	**From:** Christine Ford, R.Ph. Regulatory Project Manager
Company: Novartis Pharmaceuticals Corp.	Division of Pulmonary, Allergy, and Rheumatology Products
Phone: 862-778-1159	**Fax number:** 301-796-9728
Email: bisola.ashiru@novartis.com	**Phone number:** 301-796-3420

Subject: NDA 207923 Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules
FDA request for information from Office of Scientific Investigations

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

Comments: ***Information requested by no later than cob Friday, April 17, 2015***

Please call or send an email to confirm receipt at christine.ford@fda.hhs.gov

Document to be mailed: YES ☑ NO

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NDA 207923 for Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules is currently under review, and we have the following request for information:

Provide clinical study subject listings (a through g below) to capture the following, as applicable, and as two separate pdf files for the following sites (investigator Dr. James Pearle, Fullerton, CA):

Site #5013 in Study A2317
Site #5071 in Study A2318

a. Subject discontinuations (if applicable, sorted by treatment group and including the following variables: site subject number, screening visit date, randomization date, date of first dose/last dose, date of discontinuation, reasons for discontinuation)
b. Subject assignment per treatment arm (randomization group, as applicable)
c. Any protocol deviations or violations
d. All adverse events - if applicable per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE) [yes/no], death [yes/no]
e. Primary study efficacy endpoint
f. Relevant study efficacy endpoint/s (SGRQ scores)
g. Concomitant medication list (non-study medications)

Submit the requested information as an official response to the NDA no later than close of business Friday, April 17, 2015, or provide a timeline for when the information will be submitted.

If you have any questions, please contact Christine Ford at 301-796-3420.

Drafted by: AOrencia/ 4.7.2015
cford/ 4.7.2015

Initialed by: SBarnes/ 4.8.2015
ETorjusen/ 4.9.2015
LGilbert-McClain for BKarimi-Shah/ 4.9.2015
AOrencia/ 4.10.2015

Finalized: cford/ 4.10.2015

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/s/

CHRISTINE H CHUNG
04/10/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207923

FILING COMMUNICATION -
NO FILING REVIEW ISSUES IDENTIFIED

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 100
East Hanover, NJ 07936-1080

Attention: Bisola Ashiru Filchak, MPH
Director, Drug Regulatory Affairs

Dear Ms. Filchak:

Please refer to your New Drug Application (NDA) dated and received December 29, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules.

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 29, 2015.

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 October 1, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We have however identified CMC deficiencies that may be addressed by your response to the following requests for information:

1. Modify your acceptance criteria for particle size distribution of the following materials to more accurately reflect the range of the data from the batches used to manufacture the critical clinical batches and commercial scale registration batches (ref. Table 8-1):

(b) (4)

Lactose, [redacted]

Magnesium Stearate, [redacted]

2. Revise your analytical method for Aerodynamic Particle Size Distribution by [redacted] to remove the allowance of [redacted] inhalation, and utilize a target flow rate through the cascade impactor [redacted]. A total volume [redacted] is excessive with respect to the typical volume of air withdrawn through such products by patients during use. In addition, propose acceptance criteria for your [redacted] which reflect the data obtained under the new operating conditions.
3. Revise your analytical method for Delivered-Dose Uniformity by [redacted] to utilize a target flow rate through the cascade impactor [redacted].
4. Institute a stratified sampling plan throughout the filling process in the dosage form manufacturing process which includes in-process controls for Aerodynamic Particle Size Distribution (APSD) and Delivered Dose Uniformity (DDU). Include additional sampling and testing after any significant event has occurred. A significant event is an operation that can affect the integrity of the in-process materials and, hence, their quality attributes (e.g., [redacted]). We believe this is necessary since the [redacted] in the formulation and, as such, [redacted] during the capsule filling process which may influence these parameters, and therefore safety and efficacy. Provide an updated Master Batch Record which includes the above sampling.
5. Provide the results of stratified sampling and testing, included data analysis, for APSD and DDU throughout the filling process to assure that the proposed manufacturing process does not have a significant trend toward higher or lower delivered dose, or [redacted].
6. Institute controls on blend uniformity during formulation manufacture [redacted] Include these controls as well as the associated sampling plan in the revised Master Batch Record requested above.

We request that you also submit the following additional CMC information:

7. Provide data to support the identification and assay of the extractables identified in 3.2.P.2.4.1.1.
8. Provide an updated 356h to include all manufacturing facilities for the drug substance, device and drug product. Indicate if testing is performed at the facility. For the drug product, specify the type i.e., processing, primary packaging and/or labeling are performed at the facility.
9. Add testing facilities for release and stability if they are different from the manufacturing locations.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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(s) 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 Christine Ford, Regulatory Project Manager, at (301) 796-3420.

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

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/s/

BADRUL A CHOWDHURY
03/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207923

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 100
East Hanover, NJ 07936-1080

Attention: Bisola Ashiru Filchak, MPH
Director, Drug Regulatory Affairs

Dear Ms. Filchak:

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: Seebri Neohaler (glycopyrrolate) Inhalation Powder Hard Capsules

Date of Application: December 29, 2014

Date of Receipt: December 29, 2014

Our Reference Number: NDA 207923

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 27, 2015, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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, Allergy, and Rheumatology 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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Ford, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CHRISTINE H CHUNG
01/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 48655

MEETING MINUTES

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

Attention: Bhavini Patel, Pharm.D
Senior Global Program Regulatory Manager
Drug Regulatory Affairs

Dear Dr. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NVA237 (glycopyrronium bromide).

We also refer to the meeting between representatives of your firm and the FDA on September 28, 2011. The purpose of the meeting was to discuss your clinical studies in support of a NDA submission for NVA237.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2284.

Sincerely,

{See appended electronic signature page}

Angela Ramsey, RN, MSN
Senior Regulatory Project Manager
Division of Pulmonary, Allergy and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 28, 2011
Meeting Location: White Oak, Building 22, Conference Room 1417

Application Number: IND 48655
Product Name: NVA237 (glycopyrronium bromide)
Indication: COPD
Sponsor/Applicant Name: Novartis Pharmaceuticals

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Angela Ramsey R.N., M.S.N

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Division Director
Angela Ramsey, RN, MSN, Senior Regulatory Project Manager
Robert Lim, MD., Clinical Reviewer
Theresa Michele, MD, Clinical Team Leader
Liang Zhao, Clinical Pharmacologist Reviewer
Arthur Shaw, Chemistry Reviewer
Alan Schroeder, Chemistry Lead
Prasad Peri, Chemistry Branch Chief
Suresh Doddapaneni, Ph.D., Clinical Pharmacology Team Leader
Robert Abugov, Statistical Reviewer
Joan Buenconsejo, Statistical Team Leader

SPONSOR ATTENDEES

Linda Armstrong, M.D. Drug Safety and Epidemiology, Therapeutic Area Safety Lead
Donald Banerji, M.D., Respiratory Clinical Development, Sr. Global Program Medical Director
Jonca Bull, M.D. Drug Regulatory Affairs, US Head, Policy & Liaison
Hungta Chen, Ph.D. Integrated Information Science, Associate Director
Paul Colthorpe, Ph.D. Development, Global Program Head (NVA237)
Eric Couture, Ph.D Drug Regulatory Affairs, Global Head, Respiratory
Anton Drollmann, M.D. Clinical Pharmacology, Translational Medicine
Hans-Juergen Fuelle, M.D., Ph.D., Drug Regulatory Affairs, Global Therapeutic Area Lead
Michael Looby, Ph.D. Modeling and Simulation
David Morris, M.D. Development, Respiratory, Global Head

Tim Overend, Ph.D. Respiratory Clinical Development, Global Program Medical Director
Francesco Patalano, M.D. Development, Global Program Head (QVA149)
Bhavini Patel, Pharm.D. Drug Regulatory Affairs, Global Program Regulatory Manager
Didier Renard, Ph.D. Modeling and Simulation
Peter Rueegg, M.D., Drug Safety and Epidemiology
Romain Sechaud, Ph.D., Drug Metabolism and Pharmacokinetics
Nicholas Self-Pierson, M.S., Drug Regulatory Affairs, Global Program Regulatory Director
Donald Stanski, M.D. Modeling and Simulation, Global Head
Thomas Kieckbusch, Ph.D. Project Leader, Technical Research and Development
Thomas Martin, M.D. Respiratory Clinical Development, CSU Head

BACKGROUND

Novartis submitted a Type B meeting request dated, June 24, 2011 to discuss their clinical studies in support of a NDA submission for NVA237 in the treatment of COPD. Novartis submitted their briefing package dated, August 30, 2011. Upon review of the material, the Division responded via fax on September 27, 2011. Novartis requested to continue the face-to-face meeting to discuss response to Question 1.

The content of the email is below. Any discussions that occurred during the meeting are captured directly under the relevant response. The sponsor's questions are in ***bold italics;*** the Division's response is in *italics;* and the discussion is in normal font.

DISCUSSION

Clinical

Question 1:
Novartis believes the NVA237 clinical development program has adequately characterized the dose and dosing regimen, (b) (4) ***Does the Agency agree?***

FDA Response:
No, we do not agree. In previous FDA-Novartis interactions, we have voiced our concerns regarding your dose selection and dose selection strategy [EOP2 (7/29/08), Type A meeting/SPA denial (7/13/09), EOP2A (1/29/10)] .The results from NVA237 trial A2208 do not mitigate these concerns.

(b) (4)

(b) (4)

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(b) (4)

[redacted]

Device Interchangeability

Question 2:
Novartis believes that the user handling study and in vitro device interchangeability study have adequately investigated the potential for device interchangeability, and proposes to discourage potential misuse in patients from using the device that is not supplied with NVA237 by providing multiple and prominent differentiating (coded) features (b) (4) [redacted] ***and appropriate prescriber and patient labeling. Does the Agency agree with this approach?***

FDA Response:
Yes, this approach appears reasonable pending resolution of the issues of dose and safety raised in question 1. We agree with your approach to minimize patient mis-matching/misuse of capsule to device.

Discussion:
No discussion occurred.

Regulatory

Question 3:
Does the Agency agree with the overall proposed content and format of the NDA?

FDA Response:
Your question is premature at this time. See response to Question 1.

Discussion:

No discussion occurred.

Question 4:
Novartis requests a waiver for conducting trials in pediatrics as COPD does not occur in this population. Does the Agency agree to grant a waiver for NVA237 from the requirements of the Pediatric Research Equity Act for patients under 18 years of age?

FDA Response:
Your stated rationale appears reasonable; however, official determination will be made during the NDA review cycle. The issues raised in question 1 must be addressed prior to the NDA submission.

Discussion:
No discussion occurred.

Overall Format/Content – Clinical / PK / Statistics

Question 5:
Does the Agency agree with the proposed safety database to be included in the original NDA?

FDA Response:
We do not agree. (b) (4)

Discussion:
No discussion occurred.

Question 6:
Does the Agency agree with the safety information planned to be included in the 120-Day safety update?

FDA Response:
Your question is premature at this time. See response to Question 1.

Discussion:
No discussion occurred.

Question 7:
Does the Agency agree with the proposed content and format of the SCE (Summary of Clinical Efficacy), including the pooling strategy?

FDA Response:
For the SCE, you propose pooled analyses of Phase 3 trials A2303 and A2304. This is acceptable. However, note that label claims without statistical significance in both trials analyzed separately will be a review issue.

Discussion:
No discussion occurred.

Question 8:
Does the Agency agree with the proposed content and format of the SCS (Summary of Clinical Safety), including the pooling strategy?

FDA Response:
Your question is premature at this time. See response to Question 1. For submissions of safety data, we recommend that you collapse MedDRA preferred terms for adverse events of interest in addition to providing preferred terms. At a minimum, provide collapse terms for myocardial infarction, atrial flutter/ fibrillation, angina, stroke, congestive heart failure, tachycardia, and pneumonia, as well as other events as appropriate. As part of the NDA, provide a summary of your collapsing methodology. Also include an analysis of Major Adverse Cardiac Events (MACE).

Discussion:
No discussion occurred.

Question 9:
Novartis plans to submit the narrative portion of the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) in Modules 2.7.3 SCE and 2.7.4 SCS respectively, with the appendices of data and integrated analyses in Module 5. Does the Agency agree with this proposal?

FDA Response:
Your question is premature at this time. See response to Question 1.

Discussion:
No discussion occurred.

Reference ID: 3027523

Question 10:
Does the Agency agree with the proposals for providing the clinical and PK datasets in the NDA?

FDA Response:
Your proposal to submit complete data sets for all completed Phase 3 studies appears reasonable.

Discussion:
No discussion occurred.

Question 11:
Does the Agency agree with the proposal for submission of CRFs and SAE narratives?

FDA Response:
Your question is premature at this time. See response to Question 1.

Discussion:
No discussion occurred.

Question 12:
Does the Agency agree with the proposal for submission of CRTs?

FDA Response:
Your proposal to submit case report tabulations with data definition files and annotated case report forms for each clinical study appears reasonable.

Discussion:
No discussion occurred.

Question 13:
The submission will include 5 clinical studies conducted by Arakis Ltd and Vectura Group plc (the previous IND sponsor) in which NVA237 was administered via a different device, (b) (4) ***. These studies will be used as supportive data, and are not planned to be pooled with the NVA237 Concept1 studies. For the 5 supportive studies utilizing the*** (b) (4) ***Novartis proposes:***

- ***CSRs will be included in the original submission,***
- ***CRFs for patients who experienced an event for which a narrative is prepared will be included in the original submission (refer to Question 11),***
- ***Case report tabulations and datasets will not be included in the original submission,***
- ***Financial disclosure information for the investigators collected by the study sponsor at the time of the study will not be included as the studies would not be considered 'covered' clinical studies per the FDA guidance.***

Reference ID: 3027523

Does the Agency agree with this proposal regarding the 5 clinical studies utilizing the (b) (4) ***?***

FDA Response:
Your question is premature at this time. See response to Question 1.

Discussion:
No discussion occurred.

ATTACHMENT:

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Reference ID: 3027523

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/s/

ANGELA H RAMSEY
10/12/2011

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	B
Meeting Category:	End of Phase II
Meeting Date and Time:	July 15, 2008; 1-2:30pm
Meeting Location:	Building 22, Room 1415
Application Number:	48655
Product Name:	NVA 237
Received Briefing Package	June 13, 2008
Sponsor Name:	Novartis Pharmaceuticals, Inc.
Meeting Requestor:	Bisola Ashiru, MPH
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder:	Miranda J. Raggio, R.N., B.S.N., M.A.
Meeting Attendees:	
FDA Attendees:	Badrul A. Chowdhury, M.D., Ph.D., Division Director, Division of Pulmonary and Allergy Products
	Lydia Gilbert-McClain, M.D., Medical Team Leader, Division of Pulmonary and Allergy Products
	Robert Boucher, M.D., Medical Reviewer, Division of Pulmonary and Allergy Products
	Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products
	Larry Sancilio, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products
	Wei Qiu, Ph.D., Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
	Partha Roy, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
	Prasad Peri, Ph.D., Pharmaceutical Assessment Lead, Division of Pre- Marketing Assessment I, Branch II

Qian Li, Sc.D., Biostatistics Team Leader, Office of Biostatistics, Division of Biometrics II

Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees:

Michael Dolker, Ph.D., Biostatistics

Donald Banerji, M.D., Clinical Development

Romain Sechaud, Ph.D., Drug Metabolism and Pharmacokinetics

Bisola Ashiru, M.P.H., Drug Regulatory Affairs

Nicholas Self-Pierson, M.Sc., Drug Regulatory Affairs

Eric Coutrue, Ph.D., Drug Regulatory Affairs

Peter Fernandes, M.Pharm. Drug Regulatory Affairs

Soraya Madani, Ph.D., Drug Regulatory Affairs

Fred Marcella, M.S., Drug Regulatory Affairs, CMC

Stephen Dawe, Ph.D., Project Management

Renee Bergeron, Ph.D., Safety Assessment and Profiling

Siobhan Keating, Ph.D., Technical Research and Development

Anon Franz Drollman, M.D., Translation Medicine

BACKGROUND

Novartis Pharmaceuticals requested a Type B End-of-Phase II meeting in correspondence dated April 28, 2008, received April 29, 2008. The purpose of this meeting was to discuss the clinical and non-clinical development program for NVA237 prior to initiating the Phase III program. The meeting package was submitted to the Division on June 13, 2008. Upon review of the meeting package, the Division provided responses to Novartis via telephone facsimile on June 10, 2008. The content of telephone facsimile is printed below, with the Division's responses in ***bold italics*** and the Novartis questions in normal font. Novartis sent a power point presentation via email on July 14, 2008, which contained clarification points for each question Novartis wished to discuss at the meeting.

Summary comments of the meeting discussion are found in *italics* following the facsimile. The complete Novartis slide presentation is attached.

QUESTIONS AND RESPONSES

Question 1a: Non-clinical drug metabolism and pharmacokinetics - NVA237 enantiomers in vivo:

Does the Agency concur that the planned non-clinical pharmacokinetic package is adequate to address the fate of the NVA237 enantiomers in vivo?

Division Response: ***Yes. The planned non-clinical pharmacokinetic package supports the fate of the NVA237 enantiomers in vivo in animals provided that the bioanalytic-enantio specific method is acceptable.***

Discussion: Novartis presented the following in Slide #1:

- *Novartis has developed and fully validated the bio-analytical assay to determine both enantiomers in human urine*
    - *Subsequently, this method was adapted and validated to measure both enantiomers in plasma of dogs and rats*
    - *The concentration in human urine, dog and rat plasma was successfully determined in clinical and preclinical studies respectively as outlined in the BB*
        - *The LLOQ of the enantio-specific assay in human urine is 250 pg/mL, and 1000 pg/mL in rat and dog plasma*

The current assay does not allow measurement of the very low concentrations of both enantiomers observed in human plasma following inhalation of NVA237.

The Division stated that this approach was acceptable.

Question 1b: Non-clinical drug metabolism and pharmacokinetic package:

Does the Agency concur that the Novartis non-clinical drug metabolism and pharmacokinetic package, that includes the studies mentioned under Question 1a, the new in vitro biotransformation data, and published data from the scientific literature is adequate to support the NDA?

Division Response: ***Yes, we concur****.*

Discussion: No further discussion.

Question 2a: Clinical drug metabolism and pharmacokinetics - NVA237 enantiomers in humans:

Does the Agency concur that the planned clinical pharmacokinetic program is adequate to address the fate of the NVA237 enantiomers in human?

Division Response: ***In addition to the characterization of NVA237 enantiomers in urine, you are encouraged to develop a more sensitive assay to measure the plasma concentrations of each enantiomer.***

Discussion: Novartis presented the following in Slide # 2:

- *After intravenous administration of glycopyrronium bromide, approximately 85% was excreted mostly unchanged in urine*
- *By measuring the amount of the enantiomers excreted in urine, the elimination of the enantiomers can be characterized adequately, given that NVA237 is primarily excreted in urine*
- *LLOQ of the enantio-specific assay for urine is 250 pg/mL*
- *Urine concentrations of enantiomers were detected in high-dose groups, 100 and 200 µg in the clinical pharmacokinetic studies*

The Division commented on the importance of determining enantiomers of NVA237 in plasma. Novartis stated that they would continue to try to develop an assay to measure plasma concentrations of each enantiomer.

Question 2b: Clinical drug metabolism and pharmacokinetic package:

Does the Agency concur that the clinical drug metabolism and pharmacokinetic package, including the studies mentioned under Question 2a, is adequate to support the NDA?

***Division Response:* In addition to the planned studies, you should assess the induction potential of NVA237 on major P450s, as well as inhibition and induction potential on Pgp. The need for in vivo DDI studies should be determined based on the results from the in vitro studies. In the renal impairment study, we recommend that you include end stage patients with and without dialysis.**

Discussion: Novartis acknowledged the comments with regards to the evaluation of the effect on P450s and Pgp and presented the following in Slide # 4:

- *The patient population is composed of Group 1 – Group 4 renal impairment will be included in the study*
- *The inclusion criteria will be amended to allow end-stage patients with dialysis. However, only a limited number, if any will be enrolled given the difficulties recruiting such patients*

The Division acknowledged the sponsor's plan. No further discussion occurred.

Question 3: Adequacy of non-clinical package:

Does the Agency agree that the proposed non-clinical program provides adequate data to qualify and support Phase III and registration for NVA237?

***Division Response:* Yes, we agree, provided that acceptable (GLP) reproductive toxicity studies, a premating to conception and implantation study in rats (Segment I), a prenatal and postnatal Study in rats (Segment III), and an embryo-development study in rabbits (Segment II) are included in the NAV237 NDA submission. If any of these studies are referenced from the 1974 Robinul NDA, rights of reference must be provided.**

Submit an amended report of the 13-week rat inhalation toxicology study, which describes the epithelial hypertrophy observed at the bronchioloalveolar junction.

Clinical trials longer than four weeks need to be supported by inhalation toxicity studies in rats and dogs of adequate duration per the M3 Guidance.

Discussion: Novartis presented the following in slides # 5:

The nonclinical toxicology program was based on recommendations received from the FDA at the Pre-IND meeting with Arakis on June 9, 2004:

- *Only a 6-month inhalation study was required*
- *Inhalation teratology study was considered optional*
  - *Novartis conducted the study in rats*
- *Pending the outcome of the 6-month study and genotoxicity study, a single carcinogenicity study may be required*

- *NVS conducted carcinogenicity studies although genotoxicity studies were negative and there were no preneoplastic lesions*

- *NVA237 will be filed via a 505(b)(2) application*

The Division noted that its' pre-meeting response to question #3 was based on the understanding that Novartis would submit the NDA as a 505(b)(1) application. With the clarification that the application would be a 505(b)(2) submission, the right of reference to these reproductive toxicology studies of interest are not required, pending advice from the FDA's legal team.

Novartis informed the Division that for a 505 (b)(2) submission, a right of reference would not be required for the planned NDA, using data from the public domain. The Division remarked that if this public domain information all comes from FDA sources, the legality of the submission may be questioned, noting that recent 505(b)(2)submissions have been challenged in court. The Division told Novartis that decisions made by the FDA legal team are on a case-by-case basis and occur near the end of the review cycle.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at http://www.fda.gov/cder/guidance/guidance.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. In this case, you should establish a "bridge" (e.g., relative bioavailability study) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is appropriate. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Novartis presented the following in slide #6:

- *The amended report for the 13-week rat inhalation study will be submitted by the end of 2008*
- *Longer terms studies (a 6-month rat, a 9-month dog, and 2 carcinogenicity studies) will be provided as outlined in the BB*

No further discussion occurred.

Question 4: Toxicology qualification of individual enantiomers:

Does the Agency agree that the data provided for the individual enantiomers as well as the toxicity studies performed, ongoing and planned with the racemic mixture (b) (4) are adequate to register NVA237 as a racemic mixture?

Division Response: ***Yes, we agree.***

Discussion: No further discussion.

Question 5. Dose-selection for Phase III:

Does the Agency agree that [redacted] (b) (4) represents the optimal dose for progression into Phase III?

Division Response**: We are uncertain that* [redacted] (b) (4) ***represents the optimal dose for progression into Phase 3. [redacted] (b) (4)

Discussion: Novartis presented justification and rationale for [redacted] (b) (4) *in slide #7:*

[redacted] (b) (4)

(b) (4)

Question 6: Phase III pivotal trial design:

Novartis plans to conduct 2 parallel-group, placebo-controlled, efficacy and safety studies in patients with moderate to severe COPD to support the registration of NVA237 for this indication. Does the Agency agree that the proposed trial designs are adequate to support registration and approval?

Division Response: In general, your proposal to conduct two Phase 3 studies of 26-weeks and 52-weeks treatment duration appears reasonable provided that you have adequate preclinical data to support the proposed dose and treatment duration.

Discussion: No slide presented; no further discussion.

Question 7: Appropriateness of Phase III primary efficacy variable and demonstration of duration of action:

Does the Agency agree that i) trough FEV_1 is an appropriate primary efficacy variable for the pivotal Phase III studies, an (b) (4)

Division Response: Your Phase 3 studies should provide data to evaluate the entire dosing interval period. (b) (4)

See response to Question 6.

Discussion: Novartis presented the following in slide # 8:

(b) (4)

Question 8a: Cardiovascular safety assessment:

Does the Agency agree with the approach to assess the cardiovascular safety of inhaled NVA237 in Phase III trials?

Division Response: Your approach to collect pre-and post-dose 12-lead ECG data at various time points throughout the 6-month pivotal and 1-year studies appears reasonable, as does your plan to collect Holter data in a subset of the total patient population at baseline and at various time points

throughout the pivotal studies. The sufficiency of Holter data in only 5% of the total patient population will be a review issue.

Discussion: *Novartis presented the following in Slide #9:*

- *Novartis proposes to increase the Holter monitoring to 10% of patient population in the 2 Phase III pivotal studies to approximately 150 patients*

The Division confirmed that this plan appears to be satisfactory.

Question 8b: QTc Study:

Does the Agency agree that no further specific studies such as a dedicated QTc-trial are required for the registration of inhaled NVA237?

Division Response: We note your justification for proposing to not conduct a dedicated trial but we cannot agree at this time.

The need for a thorough QTc study for the registration of inhaled NVA237 will be a review issue.

Discussion***:*** *Novartis presented the following in slide # 10:*

- *The systemic exposure from the currently approved dosage form (oral tablets and intravenous.) exceeds the exposure expected by systemic absorption of the inhaled form by more than 50-fold*
- *Novartis would like to clarify the Agency view on the need for a QTc study*

The Division confirmed that the proposal supports the plan that no QTc study is necessary.

Question 9: Drug Substance – starting materials:

Novartis seeks FDA agreement on the designation of compounds (b) (4) as regulatory starting materials. As such, we would not be required to provide information regarding manufacture of these compounds in the NDA. Does the Agency agree?

Division Response: Your proposed synthetic route does not present an adequate (b) (4) ***as the proposed starting materials. Additionally, the*** (b) (4) ***is not isolated.***

We are concerned that some starting materials (b) (4) ***are considered structural alerts (potential genotoxins). Control the levels of these materials and limit them to NMT*** (b) (4) ***mcg/total daily intake or provide qualifications studies.***

Include the (b) (4) ***in the NDA. Include the change control agreements for*** (b) (4) ***from your vendors in the NDA. Without these documents, there is no assurance that you will have a reproducible and well-characterized impurity profile in the drug substance synthesized from these proposed starting materials if the route of synthesis to these materials changes. This is particularly relevant, as there are*** (b) (4)***.***

Alternately, provide DMFs for the proposed starting material (b) (4) ***in the NDA.***

Discussion: *Novartis presented the following in slide # 11:*

- *NVS currently controls unspecified impurities to not more than (b) (4)% which is more stringent than NMT (b) (4) mcg/total daily intake*
- *(b) (4) is not used by suppliers evaluated thus far. Suppliers intended for manufacture of commercial supplies do not use this route.*
- *SM suppliers are obligated to inform NVS of a change in the route of synthesis and test methods for starting materials must be reviewed for appropriateness i.e. potential by-products will be assessed.*

Novartis asked if the Division's comments in Question #9 pertain to only (b) (4), as well. The Division indicated that it has taken into account the fact that (b) (4) are commercially available, noting that the number of steps is very few for all (b) (4) ingredients. However, the decision is based on the fact that the drug substance has been known for more than 30 years, is well characterized and commercially available. (b) (4) did not indicate the possibility of forming any degradants that possess structural alert impurities from the synthetic route; therefore, (b) (4) is acceptable as a starting material.

The Division acknowledged that (b) (4) is a genotoxic compound and is a known mutagen, but is also a well known compound in the literature and is a simple molecule. The Division went on to say that the main issue it has with (b) (4) is that both the routes of synthesis lead to forming of impurities that are considered structural alerts. Novartis indicated that they will not use the (b) (4) route, but the Division pointed out that (b) (4) used in the other route are considered structural alerts, as well. The Division stated that they would need to fix the synthesis of this material in the NDA or provide a DMF for this compound. Novartis agreed that they would provide the synthesis for (b) (4) in the NDA. The Division emphasized that the current thinking is that (b) (4) cannot be called a starting material.

Question 10a: Aerodynamic particle size distribution (APSD) testing:

For aerodynamic particle size distribution (APSD) testing, Novartis proposes to use a flow rate of (b) (4) L/min to achieve a pressure drop as close as possible to (b) (4) while still achieving sonic flow. Does the Agency agree that the proposed flow rate is suitable from a regulatory standpoint?

***Division Response:* Your proposal to use (b) (4) L volume for APSD testing is acceptable.**

1. *Provide in the NDA the calculation for the cut off diameter for each stage of the (b) (4) at the proposed flow rate of (b) (4) L/min.*
2. *We recommend using five different devices using five different capsules (one capsule per device if there is adequate sensitivity) for APSD determination.*

Discussion: Novartis presented the following in slide # 12:

- *The cut-off diameters for each stage at (b) (4) L/min will be provided in the NDA with reference to (b) (4)*
- *NVS agrees to use 5 different devices and appropriate number of capsules to account for sensitivity for APSD for clinical release and registration stability*

No further discussion.

Question 10b: Dose uniformity testing:

For delivered dose uniformity testing Novartis currently uses and proposes to continue using a volume of (b) (4)L. Does the Agency agree that the proposed volume is suitable from a regulatory standpoint?

Division Response: Indicate if there are any differences in the DDU by using 2L and (b) (4)L volume by providing performance data.

The Agency usually recommends using a 2L volume DDU testing.

To assess inter-device variability, use ten capsules in ten different devices for DDU testing (one capsule per device).

Provide validation data for the in vitro DDU and APSD assays, as well as information to show that the manufacturing process is well controlled.

Discussion: Novartis presented the following in slide # 13:

- *Novartis agree to perform a one-time performance study comparing 2L and (b) (4)L volumes, and to provide the results in the NDA. If comparability is demonstrated, does FDA agree that (b) (4)L is acceptable?*
- *NVS will conduct appropriate development pharmaceutical studies and propose to perform a one-time study with 3 device batches in order to assess inter-device variability. NVS proposes that inter-device testing not be included as part of routine testing for drug product*
- *Analytical method validation data will be provided in Ph III IND update. Information on in-process controls will also be part of the Ph III IND; manufacturing section*

Novartis asked if the one time characterization study would provide justification for them using the (b) (4) L as a volume for DDU to match the volume used for APSD. Novartis stated that the (b) (4)L methodology was suggested as this methodology was used for the previous Novartis product, (b) (4) The Division indicated that it has always recommended using 2L for DDU and that if there were issues of powder being left over in the capsule, it has allowed labeling to indicate that a second inhalation may be made from the same capsule. However, without seeing the results DDU with 2L and (b) (4)L volume, the Division stated that it cannot comment on the acceptability of the (b) (4)L at this time.

The Division clarified for Novartis's that they should test 10 devices with 10 different capsules. Novartis claimed that this method was also used for their other product (b) (4) and that the "intra-device variability" will not be captured by using the Division's proposed methodology. The Division indicated that it is more concerned about inter-device variability than intra-device variability and stated that it has always recommended this approach for single dose DPIs. The Division also noted that intra-device variability may also be judged by the APSD measurement, which Novartis claim uses four capsules for each device.

ADDITIONAL COMMENTS

Clinical

1. ***Consider exploration of different dosing frequencies (e.g. bid, tid, etc) (b) (4) l. Refer to our response to Question 5.***

Discussion: Novartis presented the following in Slide #14:

- (b) (4)
-

No further discussion.

Chemistry

1. ***Include particle size distribution in the specifications for the (b) (4) drug substance.***

Discussion: Novartis presented the following in slide # 15:

- *Novartis is conducting (b) (4) studies with drug substance of different particle size distributions and propose to provide this data in the NDA.*
- *If this study confirms the particle size distribution of the (b) (4) is within specification then Novartis will include a particle size specification for the (b) (4) only. Based on the experience of different batches of (b) (4) drug substance, we can conclude that the (b) (4) process is robust with respect to particle size of the (b) (4) drug substance*

Novartis clarified that the (b) (4) is the (b) (4) drug substance. The Division indicated that the proposal by Novartis seems reasonable but that it cannot agree that the proposal is acceptable until the data in the NDA are reviewed.

The Division asked if the Spiriva capsule will fit in the Novartis device. Novartis responded that this possibility had not been evaluated. The Division indicated that the issue of device interchangeability will need to be addressed, and emphasized that this issue will have an impact on the action taken. The Division noted that Novartis stated that only their own development program could use the Concept 1 inhaler, but, in fact, there are other development programs that could potentially use this device. Novartis claimed that this issue could be addressed by labeling.

Post meeting comment:

The Division does not consider "intra-device" variability for single dose DPIs because the capsules are already pre-metered. This variability is more critical when a device is relied upon to meter the individual dose as opposed to using capsules which are pre-metered.

If you have any questions, please contact Miranda Raggio, Regulatory Project Manager, at 301-796-2109.

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Linked Applications	Sponsor Name	Drug Name
IND 48655	NOVARTIS PHARMACEUTICALS CORP	NVA237 GLYCOPYRRONIUM BROMIDE

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/s/

MIRANDA B RAGGIO
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