

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

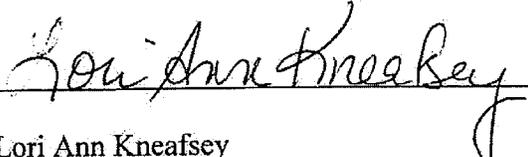
*APPLICATION NUMBER:*  
**200045Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**Patent Certification**

**Paragraph II Certification**

In Novartis' opinion, and to the best of our knowledge, there are no unexpired patents covering amlodipine besylate or hydrochlorothiazide.

  
Lori Ann Kneafsey

2-18-2010  
Date

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use**

NDA NUMBER

200045

NAME OF APPLICANT/NDA HOLDER

Novartis Pharmaceutical Corporation

**The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.**

TRADE NAME (OR PROPOSED TRADE NAME)

(b) (4)

ACTIVE INGREDIENT(S)

aliskiren/amlodipine/hydrochlorothiazide

STRENGTH(S)

150/5/12.5 300/10/12.5  
300/5/12.5 300/10/25  
300/5/25

DOSAGE FORM

tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,559,111

b. Issue Date of Patent

03/15/2014

c. Expiration Date of Patent

July 21, 2018

d. Name of Patent Owner

Novartis Corporation

Address (of Patent Owner)

608 Fifth Avenue

City/State

New York, NY

ZIP Code

10020

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

One Health Plaza

City/State

East Hanover

ZIP Code

07936

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes  No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes  No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Claim 9	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) A method of treating hypertension
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**5. No Relevant Patents**

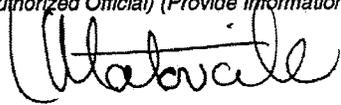
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**



Date Signed

02/15/2010

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Lisa M. Matovcik

Address

One Health Plaza

City/State

East Hanover, NJ

ZIP Code

07936

Telephone Number

(862) 778-5442

FAX Number (if available)

(973) 781-8064

E-Mail Address (if available)

lisa.matovcik@novartis.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer (HFA-710)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

NDA # 200045

SUPPL #

HFD # 110

Trade Name Amturnide

Generic Name amlodipine/aliskiren/hydrochlorothiazide

Applicant Name Novartis

Approval Date, If Known December 21, 2010

### 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)(2)

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

YES  NO

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

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:

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA# 19787 amlodipine besylate

NDA# 21985 aliskiren

NDA# 16042 hydrochlorothiazide

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:

SAH2302

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"):

SAH2302

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

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

Investigation #1  
IND # 101386      YES       !  
!      ! NO   
! Explain:

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

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

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

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: Lori Anne Wachter  
Title: Regulatory Project Manager  
Date: December 22, 2010

Name of Office/Division Director signing form: Norman Stockbridge  
Title: Division Director

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

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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.**  
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/s/  
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Lori A WACHTER  
12/22/2010

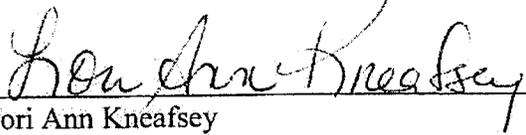
NORMAN L STOCKBRIDGE  
12/22/2010

## **1 Waiver for Pediatric Studies**

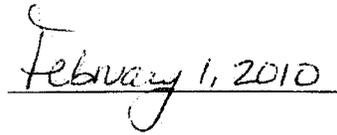
Pediatric data will not be included in this application for aliskiren/amlodipine/hydrochlorothiazide (SAH100) fixed dose combination tablets which is being evaluated for the treatment of essential hypertension. The Division previously waived the pediatric requirement for other aliskiren fixed dose combination products on the basis that data in pediatric patients will not be available for each of the components at the projected time of submission. Therefore, we request a waiver of the pediatric requirement for this combination. Please confirm that the request for a pediatric waiver is acceptable to the Pediatric Review Committee (PeRC) and Cardio-Renal Division.

**Debarment Certification**

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Lori Ann Kneafsey  
Associate Director  
Drug Regulatory Affairs



Date

**NDA No. 200-045**

**SAH100** [REDACTED] (b) (4)

[REDACTED] (b) (4)

**Film-Coated Tablets**

**Field Copy Certification**

Novartis Pharmaceuticals Corporation hereby certifies that the field copy of this submission is a true copy of the Chemistry, Manufacturing and Controls technical section; application form; and summary (as applicable) contained in the electronic archival copy of the same application. The field submission copy is being provided to the appropriate Pre-Approval Inspection coordinator, concurrent with the NDA, through notification of electronic access by copy of the NDA cover letter and Field Copy Certification Statement.



\_\_\_\_\_  
Fernando Marcella M.S., RAC  
Regulatory CMC Manager  
Global Regulatory CMC

*23 Feb - 2010*

\_\_\_\_\_  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 200045 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Amturnide Established/Proper Name: amlodipine/aliskiren/hydrochlorothiazide Dosage Form: Tablet		Applicant: Novartis Agent for Applicant (if applicable): N/A
RPM: Lori Anne Wachter		Division: Cardiovascular and Renal Products
<p>NDA's: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s): amlodipine NDA 019787</p> <p>Provide a brief explanation of how this product is different from the listed drug. This product is a fixed dose triple combination.</p> <p>If no listed drug, explain. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: December 21, 2010</p> <p><b>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.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is _____</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics<sup>2</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 100px;">REMS: <input type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 400px;"><input type="checkbox"/> REMS not required</span></p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>• Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> 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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) December 21, 2010
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
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<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	Included
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	Included
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	Acceptable November 30, 2010
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM December 21, 2010 <input checked="" type="checkbox"/> DMEPA December 8, 2010 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC December 13, 2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> Not a (b)(2) December 6, 2010 <input type="checkbox"/> Not a (b)(2) December 6, 2010
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)               <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>June 30, 2010</u> If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input checked="" type="checkbox"/> Verified, statement is acceptable

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
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❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    December 21, 2010
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None    December 10, 2010
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	December 10, 2010
• Clinical review(s) ( <i>indicate date for each review</i> )	November 23, 2010
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
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<b>Clinical Microbiology</b>		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None
<b>Biostatistics</b>		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None November 23, 2010
<b>Clinical Pharmacology</b>		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None November 24, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )		<input checked="" type="checkbox"/> None
<b>Nonclinical</b>		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )		<input type="checkbox"/> None July 7, 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )		<input checked="" type="checkbox"/> None requested
<b>Product Quality</b>		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) ( <i>indicate date for each review</i> )		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) ( <i>indicate date for each review</i> )		<input type="checkbox"/> None April 23, 2010
• Product quality review(s) including ONDQA biopharmaceutics reviews ( <i>indicate date for each review</i> )		<input type="checkbox"/> None November 2, 2010
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) ( <i>indicate date of each review</i> )		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) ( <i>indicate date of each review</i> )		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer ( <i>indicate date of each review</i> )		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	
<input checked="" type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	December 8, 2010
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: December 16, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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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.**  
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/s/  
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Lori A WACHTER  
12/22/2010



NDA 200045

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs

Dear Ms. Kneafsey:

Please refer to your New Drug Application (NDA) dated February 25, 2010, received February 25, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aliskiren, Amlodipine Besylate, and Hydrochlorothiazide Tablets, 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/5 mg/25 mg, 300 mg/10 mg/12.5 mg, and 300 mg/10 mg/25 mg.

We also refer to your November 12, 2010, correspondence, received November 15, 2010, requesting review of your proposed proprietary name, Amturnide. We have completed our review of the proposed proprietary name, Amturnide and have concluded that it is acceptable.

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

If **any** of the proposed product characteristics as stated in your November 12, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lori Wachter at 301-796-3975.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
12/21/2010



NDA 200045

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

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

ATTENTION: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs

Dear Ms. Kneafsey:

Please refer to your New Drug Application (NDA) dated February 25, 2010, received February 25, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aliskiren, Amlodipine Besylate, and Hydrochlorothiazide Tablets, 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/5 mg/25 mg, 300 mg/10 mg/12.5 mg, and 300 mg/10 mg/25 mg.

We acknowledge receipt of your October 18, 2010 correspondence, on October 18, 2010, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of October 18, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nina Ton, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Lori Wachter at 301-796-3975.

Sincerely,

*{See appended electronic signature page}*

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

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/s/  
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CAROL A HOLQUIST  
12/16/2010

**MEMORANDUM**

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

**DATE:** December 20, 2010  
**SUBJECT:** Internal Meeting Memo from December 16, 2010  
**NDA:** NDA 200045  
**PRODUCT:** Amturide  
**SPONSOR:** Novartis

**Background:** NDA 200045, Amturide is a fixed dose, triple combination of three approved drugs, for the treatment of hypertension. This meeting was requested by the sponsor to discuss several labeling issues that have arisen during labeling negotiations. Because there is a large food effect with aliskiren, the Division proposed language stating that if the patient does not achieve an adequate response on monotherapy aliskiren, the physician may want to have the patient take it fasted before adding a second or third drug. The sponsor also needs feedback on the revised carton and container labels, prior to submitting them officially. Please also see attached PI, carton, and container labels.

**FDA Participants:**

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products (DCaRP)
Mary Ross Southworth, Pharm.D.	Deputy Director For Safety, DCaRP
Abraham (Avi) Karkowsky, M.D., Ph.D.	Clinical Team Leader, DCaRP
Tsvi Aranoff, M.D.	Clinical Reviewer, DCaRP
Rajanikanth Madabushi, Ph.D.	Team Leader, Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, Ph.D.	Clinical Pharmacologist, (OCP)
Kristina Toliver, Pharm, D.	Team Leader, Division of Medication Error and Prevention
Meg Pease-Fye, M.S., RAC	Regulatory Project Manager for Safety, DCaRP
Lori Anne Wachter, R.N., B.S.N.	Regulatory Health Project Manager

**Novartis Participants:**

Caroline Boulton	Drug Regulatory Affairs
Gautier Sala	Drug Regulatory Affairs
Deborah Keefe	Clinical
Venkateswar Jarugula	Pharmacokinetics
Huang Hsu	Statistics
Fred Marcella	Regulatory CMC

**Teleconference:**

Dr. Stockbridge began the meeting by stating that the package insert is, for the most part, acceptable. There are a few minor issues that need revision. They are as follows:

Internal Meeting Memo  
NDA 200045

- Under Geriatric Use – there is a word at the end of the section that does not belong, and needs to be removed.
- Under Special Populations – the cross reference format for renal impairment, and several other cross references on that page are improper, and need revision.
- All other revisions are acceptable.

(b) (4)

There is information available stating that food decreases exposure of aliskiren several-fold. The effect is as big as or larger than the change in exposure between approved doses of aliskiren. But a recent study (#2110, submitted to IND 101386 for aliskiren/amlodipine/hydrochlorothiazide) concludes little or negligible effect of food (light fat meal) on blood pressure though the magnitude of decrease in aliskiren exposure is similar to that observed with a high fat meal.

Dr. Stockbridge asked the sponsor to explain the inconsistency between the lack of food effect and the presence of a dose-response relationship for aliskiren. The sponsor hypothesized that the extent of tissue partitioning of aliskiren could possibly account for the lack of blood pressure changes irrespective of changes in systemic exposures because of food. The sponsor further referred to tissue distribution study (#2238 also submitted to IND 101386). The sponsor stated that the dose-response relationship for aliskiren was a sigmoid shaped with a shallow slope. Hence, the sponsor hypothesizes no new safety or efficacy changes.

Dr. Stockbridge stated that it would be helpful to produce a complete, internal description correlating dose response relationship and food effect. This document will be submitted to NDA 21985 as a part of aliskiren efficacy supplement and will be reviewed. For now, there will be no Post Marketing Requirement added to the Action Letter, and the language regarding the use of aliskiren fasted before adding a second drug will not go into the Amturnide label at this time.

The discussion moved on to the container labels. Dr. Toliver had the following comments:

- The tradename color change is acceptable, but the graphics need modification – they appear too similar among the dose strengths.
- The shrink sleeve, and the dosage form no longer appear with the established name. The sponsor must add the dosage form. The graphic needs to be one half the size of the proprietary name.
- Physician samples need “per tablet” added to the label.

The sponsor will make the requested changes and send the revised label and carton and container labels to the project manager via e-mail.

Reviewed:

NS 2/7

KT 2/7/11

MPF 1/18/11

MRS 1/18/11

AK1/12/11

TA 1/11/11

RM 1/11/11

SH 1/10/11

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/s/  
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Lori A WACHTER  
02/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR DDMAC LABELING REVIEW CONSULTATION</b> <b>**Please send immediately following the Filing/Planning meeting**</b>		
TO: <b>CDER-DDMAC-RPM</b>		FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Lori Anne Wachter</b>		
REQUEST DATE <b>12/9/2010</b>	IND NO.	NDA/BLA NO. <b>200045</b>	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)	
NAME OF DRUG <b>Amturnide (amlodipine/aliskiren/HCTZ)</b>	PRIORITY CONSIDERATION <b>Standard</b>	CLASSIFICATION OF DRUG <b>Combination antihypertensive</b>	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)	
NAME OF FIRM: <b>Novartis</b>		PDUFA Date: <b>12/25/2010</b>		
<b>TYPE OF LABEL TO REVIEW</b>				
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION		REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
<b>EDR link to submission:</b>  <b>Location:            \\CDSESUB1\EVSPROD\NDA200045</b>		Deleted: <input type="checkbox"/> Deleted: <input type="checkbox"/> Formatted: French (France) Deleted: <input type="checkbox"/> Formatted: French (France) Formatted: French (France)		
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.				
COMMENTS/SPECIAL INSTRUCTIONS: <b>Please review the attached labeling.</b>				
Mid-Cycle Meeting: <b>August 31, 2010</b>		Deleted: [Insert Date]		
Labeling Meetings: <b>November 2, 2010; November 3, 2010; November 15, 2010</b>		Deleted: [Insert Dates]		
Wrap-Up Meeting: <b>November 19, 2010</b>		Deleted: [Insert Date]		
SIGNATURE OF REQUESTER <b>Lori Anne Wachter, RN, BSN</b> Regulatory Project Manager				
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one)		

	<input checked="" type="checkbox"/> eMAIL	<input type="checkbox"/> HAND

Deleted:

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/s/  
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Lori A WACHTER  
12/09/2010



NDA 200045

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Kneafsey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAH100 (aliskiren/amlodipine besylate/hydrochlorothiazide) tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Your proposed dissolution methodology for aliskiren/amlodipine and for hydrochlorothiazide is acceptable, however, the proposed specifications need to be tightened as follows:

From **Q= (b) (4) at 30 min for Aliskiren and Amlodipine**  
**Q= (b) (4) at 30 min for Hydrochlorothiazide**

To: **Q= (b) (4) at 30 min for Aliskiren and Amlodipine**  
**Q= (b) (4) at 30 min for Hydrochlorothiazide**

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAMESH K SOOD  
11/03/2010

# DSI CONSULT

## Request for Biopharmaceutical Inspections

**DATE:** April 16, 2010

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** Norman Stockbridge, MD, PhD  
Director, Division of Cardiovascular and Renal Products, HFD-110

**FROM:** Lori Anne Wachter, RN, BSN, Regulatory Project Manager, Division of Cardiovascular and Renal Products HFD-110

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 200045  
(b) (4) 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, 300/10/25 mg Tablets  
Novartis

### Study/Site Identification:

The following study/site is pivotal to approval and has been identified for inspection. It bridges the formulation used in pivotal efficacy trial to the to-be-marketed (TBM) formulation and also covers biowaiver claims for other dose levels. The clinical study site is within United States (b) (4) [redacted].

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
SAH100A2104	Bio-Kinetic Clinical Applications LLC 1816 W. Mt. Vernon Springfield, MO 65802  <b>PI:</b> Dennis Morrison, DO  417-831-0456 (Phone) 417-831-0778 (Fax) <b>E-mail:</b> Not available	(b) (4) [redacted]  <b>Contact details:</b> Not available

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **December 23, 2010**. We intend to issue an action letter on this application by **December 23, 2010**.

Should you require any additional information, please contact:

Sudharshan Hariharan  
Clinical Pharmacology Reviewer  
WO51 RM1362  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Concurrence:

Hariharan, Sudharshan (OCP Reviewer, Primary)  
Menon-Andersen, Divya (OCP Reviewer, Secondary)  
Madabushi, Rajnikanth (Team leader, Office of Clinical Pharmacology)  
Stockbridge, Norman (Division Director)

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/s/

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Lori A WACHTER  
10/05/2010



NDA 200045

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Kneafsey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SAH100 (aliskiren/amlodipine besylate/hydrochlorothiazide) tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide the linearity and accuracy information for impurity (b) (4) in the DP analytical method validation report: identity, assay, degradation products and content uniformity by HPLC.
2. It is noted that the batch analysis data were generated from the batches manufactured at Novartis E. Hanover, NJ, facility and Novartis Pharma, Stein, Switzerland, facility. The Novartis E. Hanover, NJ, facility is not a proposed commercial manufacturing site. To establish a comparable product quality, provide dissolution profile comparison (f2 values) of the products manufactured at these two sites.
3. Provide batch release data for all batches produced at the Stein Switzerland site to establish the commercial manufacturing capability of the Stein site.
4. Provide following missing information in the batch analysis data of the registration batches: (1) for the 300/5/12.5 mg strength, the information on “any unspecified impurity” was missing for all three registration batches; and (2) for the 300/10/12.5 mg strength, the information on “any unspecified impurity (b) (4) [redacted] was missing for Batch H690GF.
5. Include a footnote for aliskiren hemifumarate content in the product label, similar to the one provided for amlodipine besylate content.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/

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RAMESH K SOOD  
09/28/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): Raanan Bloom, OPS/PARS, (301)796-2185

FROM (Name, Office/Division, and Phone Number of Requestor): Don Henry  
Project Manager, ONDQA, 301-796-4227 on behalf of  
Donghao Lu/Kasturi Srinivasachar

DATE  
August 27, 2010

IND NO.

NDA NO.  
200045

TYPE OF DOCUMENT  
original submission

DATE OF DOCUMENT  
February 25, 2010

NAME OF DRUG  
Aliskiren, amlodipine,  
hydrochlorothiazide

PRIORITY CONSIDERATION  
standard

CLASSIFICATION OF DRUG  
Cardio-renal

DESIRED COMPLETION DATE  
October 25, 2010

NAME OF FIRM: Novartis Pharmaceuticals

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

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|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: A review of the environmental assessment is requested. This is an electronic submission.

SIGNATURE OF REQUESTOR  
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-200045

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ORIG-1

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NOVARTIS  
PHARMACEUTICA  
LS CORP

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 (b) (4)

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/s/  
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DON L HENRY  
08/27/2010



NDA 200045

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

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

ATTENTION: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs

Dear Ms. Kneafsey:

Please refer to your New Drug Application (NDA) dated February 25, 2010, received February 25, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aliskiren, Amlodipine Besylate, and Hydrochlorothiazide Tablets, 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/5 mg/25 mg, 300 mg/10 mg/12.5 mg, and 300 mg/10 mg/25 mg.

We acknowledge receipt of your August 5, 2010 correspondence, on August 5, 2010, notifying us that you are withdrawing your request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of August 5, 2010.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Nina Ton, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Lori Wachter at 301-796-3975.

Sincerely,

*{See appended electronic signature page}*

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

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-200045

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ORIG-1

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NOVARTIS  
PHARMACEUTICA  
LS CORP

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 (b) (4)

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/s/  
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CAROL A HOLQUIST  
08/12/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Angelica Dorantes/Patrick Marroum  
CDER/OPS/ONDQA**

FROM (Name, Office/Division, and Phone Number of Requestor): **Don Henry  
Project Manager, ONDQA, 301-796-4227 on behalf of  
Donghao Lu/Kasturi Srinivasachar**

DATE  
June 17, 2010

IND NO.

NDA NO.  
200045

TYPE OF DOCUMENT  
original submission

DATE OF DOCUMENT  
February 25, 2010

NAME OF DRUG  
**Aliskiren, amlodipine,  
hydrochlorothiazide**

PRIORITY CONSIDERATION  
standard

CLASSIFICATION OF DRUG  
Cardio-renal

DESIRED COMPLETION DATE  
October 25, 2010

NAME OF FIRM: **Novartis Pharmaceuticals**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW            |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY                |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input checked="" type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW):      |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |  |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input checked="" type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE        |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS       |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input checked="" type="checkbox"/> IN-VIVO WAIVER REQUEST |

#### IV. DRUG SAFETY

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

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

**COMMENTS / SPECIAL INSTRUCTIONS:** A review of the following information is requested: 1) the dissolution method development and acceptance criteria, 2) the BE studies for the 300/5/25 mg and 300/10/25 mg strengths, and 3) the biowaiver request for the 150/5/12.5 mg, 300/10/12.5 mg and 300/5/12.5 mg strengths based on the BE studies and the similarity in the in vitro dissolution profiles for each component in 4 different pH media.

SIGNATURE OF REQUESTOR  
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/  
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DON L HENRY  
06/21/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): <b>Nina Ton</b> <b>Mail: OSE</b>			FROM: <b>Lori Wachter, RPM</b> Division of Cardiovascular and Renal Products		
DATE <b>May 19, 2010</b>	IND NO.	NDA NO. <b>200045</b>	TYPE OF DOCUMENT <b>PPI</b>	DATE OF DOCUMENT	
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION <b>S</b>		CLASSIFICATION OF DRUG <b>Fixed dose Combination antihypertensive</b>	DESIRED COMPLETION DATE <b>June 30, 2010</b>	
NAME OF FIRM: <b>Novartis</b>					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
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<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review and provide comments regarding the PPI of the (b) (4) label.  This is an electronic submission. I will send the Word version of the label to Nina Ton via e-mail. <b>\\CDSESUB1\EVSPROD\NDA200045</b>					
SIGNATURE OF REQUESTER <b>Lori Anne Wachter, RN, BSN</b>			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
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/s/  
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Lori A WACHTER  
05/19/2010



NDA 0200045

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

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

ATTENTION: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs

Dear Ms. Kneafsey,

Please refer to your New Drug Application (NDA) dated February 25, 2010, received February 25, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aliskiren, Amlodipine Besylate, and Hydrochlorothiazide Tablets, 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/5 mg/25 mg, 300 mg/10 mg/12.5 mg, and 300 mg/10 mg/25 mg.

We also refer to your March 2, 2010, correspondence, received March 2, 2010, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lori Wachter at 301-796-3975.

Sincerely,

*{See appended electronic signature page}*

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

Application  
Type/Number

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Submitter Name

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/s/  
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CAROL A HOLQUIST  
05/19/2010



NDA 200045

**FILING COMMUNICATION**

Novartis Pharmaceuticals Corporation  
Attention: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936

Dear Ms. Kneafsey:

Please refer to your new drug application (NDA) dated February 25, 2010, received February 25, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (aliskiren/amlodipine/hydrochlorothiazide) 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg, and 300/10/25 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is December 25, 2010.

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 requirement/commitment requests by November 27, 2010.

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.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

If you have any questions, please call:

Lori Anne Wachter, RN, BSN  
Regulatory Project Manager  
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-200045

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/s/  
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NORMAN L STOCKBRIDGE  
05/05/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b> <b>Nina Ton</b>		FROM: Division of Cardiovascular and Renal Products Lori Anne Wachter, RPM		
DATE 4.8.10	IND NO.	NDA NO. <u>200045</u>	TYPE OF DOCUMENT <u>Risk Management Plan</u>	DATE OF DOCUMENT February 25, 2010
NAME OF DRUG (b) (4)	PRIORITY CONSIDERATION <u>Standard</u>	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE <u>May 31, 2010</u>	
NAME OF FIRM: <b>Novartis</b>				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
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<b>III. BIOPHARMACEUTICS</b>				
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<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: <b>Novartis submitted NDA 200045 February 25, 2010. It contains a "Risk Management Plan". Please review.</b>  <b>This is an electronic submission and can be accessed by clicking the following link: \\CDSESUB1\EVSPROD\NDA200045</b>  <b>The Risk Management Plan is found in Module 1.16 and the Label is found in Module 1.14.</b>  <b>Thank you!!</b>				
SIGNATURE OF REQUESTER Lori Anne Wachter, RN, BSN		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
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/s/  
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Lori A WACHTER  
04/08/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 101,386

ADVICE/INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Lori Ann Kneafsey  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Kneafsey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aliskiren/amlodipine/hydrochlorothiazide tablets.

We also refer to your correspondence dated September 23, 2009 requesting the Division's agreement with your proposal not to pool studies CSPP100A2360 and CSPP100A2411 with the other studies in your upcoming NDA submission.

We have the following comments and recommendations:

1. The Division agrees with your proposal not to pool studies CSPP100A2360 and CSPP100A2411 with the other studies in your submission.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

If you have any questions, please contact Mike Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

*{See appended electronic signature page}*

Norman Stockbridge, M.D., Ph.D.

Director

Division of Cardiovascular and Renal Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-101386	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	ALISKIREN/AMLODIPINE/HCTZ TABLETS

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/s/

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NORMAN L STOCKBRIDGE  
09/29/2009

**DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
CDER, DCRDP (HFD-110)  
10903 New Hampshire Ave.,  
Silver Spring, MD 20993-0002

FDA  
10903 New Hampshire Ave  
Silver Spring, MD 20993-00025600

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**Transmitted via email:** lori.bolognese@novartis.com

Attention: Lori Bolognese

**Company Name:** Novartis Pharmaceuticals Corporation

Phone:

**Subject:** IND 101,386 12 Mar 09 Pre-NDA  
Meeting (TCO) Preliminary Responses

**Date:**

**Pages including this sheet:**

**From:** CDR John David  
**Phone:** 301-796-1059  
**Fax:** 301-796-9838

**\*\*\*\*\*PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

FDA Division of Cardiovascular and Renal Products Preliminary Responses

Sponsor: Novartis Pharmaceuticals Corporation  
Drug: aliskiren/amlodipine/HCTZ Tablets (SAH100A)  
PIND: 101,386  
Date of request: January 9, 2009  
Date request received: January 9, 2009  
Date of confirmation: January 16, 2009  
Date of pre-meeting: February 26, 2009  
Date of meeting: March 12, 2009  
Time: 11 am – 12 noon

Type/Classification: B/Pre-NDA

Meeting Chair: Norman Stockbridge, M.D., Ph.D.

Meeting recorder: John David

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Shen Xiao, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Director, Division of Biometrics I, HFD-710
Jialu Zhang, Ph.D.	Statistician, HFD-710
Angelica Dorantes, Ph.D.	Clinical Pharmacology, HFD-860
Robert Kumi, Ph.D.	Clinical Pharmacology, HFD-860
Selma Lemtouni, M.D., M.P.H.	Medical Officer, HFD-110
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Kasturi Srinivasachar, Ph.D.	Chemistry Pharmaceutical Assessment Lead, ONDQA
Prafull Shiromani, Ph.D.	Chemist, HFD-110
Edward Fromm	Chief, Regulatory Health Project Manager, HFD-110
John David	Regulatory Health Project Manager, HFD-110

Background:

Novartis Pharmaceuticals plans to submit an NDA for the fixed combination of aliskiren/amlodipine/HCTZ in the first quarter of 2010 under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The sponsor notes that the NDA will contain studies conducted by Novartis in direct support of the fixed combination. The sponsor expects the fixed combination of aliskiren/amlodipine/HCTZ to provide a single-dose formulation for those patients who require additional blood pressure control beyond that obtained with aliskiren/amlodipine, aliskiren/HCTZ or amlodipine/HCTZ therapy. A Pre-IND meeting was held on March 14, 2008 regarding the development plan for this project. Aliskiren/amlodipine/HCTZ is indicated for the treatment of hypertension. Novartis proposes to develop a single tablet formulation containing aliskiren, amlodipine, and hydrochlorothiazide in the following 5 fixed dosage strengths:

- 150 mg aliskiren/5 mg amlodipine/12.5 mg hydrochlorothiazide (150/5/12.5)
- 300 mg aliskiren/5 mg amlodipine/12.5 mg hydrochlorothiazide (300/5/12.5)
- 300 mg aliskiren/5 mg amlodipine/25 mg hydrochlorothiazide (300/5/25)
- 300 mg aliskiren/10 mg amlodipine/12.5 mg hydrochlorothiazide (300/10/12.5)
- 300 mg aliskiren/10 mg amlodipine/25 mg hydrochlorothiazide (300/10/25)

*This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 12, 2009 between Novartis and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact John David), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact John David to discuss the possibility of including these for discussion at the meeting.*

**Questions for the Division:**

**Clinical / Statistical**

1. Our proposed pooling strategy for clinical efficacy and safety is noted in Section 3.2 and Section 3.3. Does the Division agree with our proposed pooling strategy for trials included in the SCS and SCE?

**Preliminary Response:** The Division agrees.

2. Novartis proposes to submit an integrated summary of clinical laboratory data in international units. Does the Division agree with this proposal?

**Preliminary Response:** The Division agrees.

3. In Section 3.4, we propose not to re-submit components (study report, patient narratives, and case report forms and SAS datasets) for study CSPP100A2344 (previously submitted to NDA 22-107/s002) and for study CSPA100A2301 which will be submitted in the aliskiren/amlodipine NDA. Does the Division agree with this proposal?

**Preliminary Response:** The Division agrees.

4. Does the Division agree with our proposal in Section 3.4 for the submission of patient narratives, CRFs and CRTs?

**Preliminary Response:** We agree with your proposal regarding patient narratives. We have the following comments regarding your proposal for the submission of CRFs and CRTs:

Regarding CRFs, please submit CRFs for all deaths and discontinuations from study or study drug regardless of presumed cause. Also, please clarify what you mean by “an electronic representation of the CRF”. If the case report form data were entered into an electronic system without being recorded first on a paper form, then we can understand the necessity of providing an electronic representation. Otherwise we require you to submit images of the paper forms used. Regardless of initial paper or electronic format, we require submission of the original entries on the CRFs as well as an audit trail of all changes. Finally, CRFs include all communications of clinical data between the investigators and you or your agents regardless of whether

they have arbitrary titles of “case report forms” or otherwise. In particular, Medwatch reports or CIOMIS forms are CRFs and must be included with the rest of the CRFs.

Regarding CRTs, please submit records for the original entries recorded by the investigators and the final entries used for the analyses. Alternatively, you may provide the final entries and a mechanism for reconstructing the audit trail of entries.

5. At the pre-IND meeting the Division agreed that the proposed clinical program is sufficient to support the registration of aliskiren/amlodipine/HCTZ at 4 dosage strengths (150/5/12.5, 300/5/12.5, 300/5/25, 300/10/25 mg). Novartis would like to add one additional dose (300/10/12.5 mg). Does the Division agree that the clinical program can also support the registration of this dose?

**Preliminary Response:** The two proposed bioequivalence studies will support the approval of the 300/10/25 and 300/5/25 strengths as well as the 150/5/12.5 mg (since this strength can be waived based on similarity of the dissolution profiles. However, it is not clear from the meeting package what will be the basis of approval for the 300/5/12.5 and 300/10/12.5 since from the composition of the active ingredients they are not considered to be proportionally similar to either dosage strengths tested in the bioequivalence studies. A better strategy would be to conduct the bioequivalence on the highest and lowest dosage strengths and obtain a biowaiver for the intermediate strengths based on similarity of the dissolution profiles in three media.

6. Does the Division agree that the proposed biopharmaceutics/clinical pharmacology studies in Section 4 are adequate to support registration of the aliskiren/amlodipine/hydrochlorothiazide fixed combination?

**Preliminary Response:** We agree in general that the outlined studies are adequate to support registration. The only area of concern is with the drug-drug interaction information. As noted during the pre-IND teleconference on March 14, 2008, the drug-drug interactions of interest are a comparison of the pharmacokinetics of each drug monotherapy to the triple drug combination.

### CMC

7. Novartis proposes to include only one executed batch record. It will be representative for all 5 strengths as the manufacturing process is the same and contains excipients common to all strengths. All batch records will be available at the site of manufacture for the pre-approval inspection. This will reduce the volume of documentation provided in the regional section (3.2.R.1) of the CTD and facilitate review. Does the Division agree with this approach?

**Preliminary Response:** The Division agrees.

(b) (4)

**Preliminary Response:** Provide representative CoAs for all excipients.

a. Novartis will provide 6 months drug product stability for strengths 150/5/12.5, 300/5/12.5, 300/5/25, 300/10/25 mg aliskiren/amlodipine/hydrochlorothiazide) and 3 months stability data for strength 300/10/12.5 mg at the time of the original NDA submission, A description of the registration stability protocol is provided in Section 6.2.8. Novartis intends to provide twelve (12) month drug product stability data for strengths 150/5/12.5, 300/5/12.5, 300/5/25, 300/10/25 mg and nine (9) month stability data for strength 300/10/12.5 mg to the Agency within <sup>(b)</sup><sub>(4)</sub> months after the submission date of the original NDA, to support an expiry period of 24 months on all strengths.

- b. Novartis intends to bracket the 90 count HDPE bottle in 120mL or 175mL bottles, depending on strength, by testing the 30 count bottle (90mL) and the 100 count bottle (120mL, 175mL, or 325mL depending on strength). The 90 count bottle configuration will not be tested.
- c. Novartis intends to conduct profile dissolution testing of the initial and 6 month stability samples at long-term room temperature conditions to define the appropriate dissolution release specifications.
- d. Since amlodipine and hydrochlorothiazide suppliers have been determined to be comparable and interchangeable, Novartis intends to use one 1 supplier for amlodipine and hydrochlorothiazide, respectively in the Registration Stability program. However, Novartis does commit that the alternative amlodipine suppliers will be evaluated in commercial drug product (when they are used) as part of our annual stability program. The data from the annual stability program will be provided in the annual report.
- e. Stability testing of Physician Sample Bottles (table 6.5) 45mL with 7 tablet count will be conducted on (b) (4) of each strength. In addition, MET (MLT) testing will not be conducted for the physician sample bottles as sufficient microbiological data will be generated with trade bottle packaging which have the same bottle quality and closure system.

Does the Division agree with this approach?

**Preliminary Response:**

- a. Provide stability update by month 5. The expiry period will depend upon the quality of the stability data;
- b. Revise the bracketing plan to include the physician sample bottles. Protective characteristics of all bottles should be equivalent;
- c. Include additional time-points, including 12 months;
- d. We agree;
- e. Stability testing should be conducted on 3 batches of each strength, unless covered by your bracketing plan. Use same testing as for commercial strengths.

9. Based on our experience during the drug development process, Novartis proposes a single media dissolution method for the release of the drug substances (Aliskiren, Amlodipine besylate, hydrochlorothiazide). Details on the dissolution method is provided in Section 6.2.5.1. Does the Division agree with this method?

**Preliminary Response:** In principle the use of one dissolution method for all three components is acceptable. However, the adequacy of the dissolution method and specifications is a review issue. A decision on the acceptability of the dissolution method and specification will be made during the NDA review. (b) (4)

10. Novartis intends to cross-reference the Tekturna (Aliskiren) Tablets NDA 21-985, and the Diovan HCT NDA 20-818, for all Aliskiren and hydrochlorothiazide drug substance information (respectively) in the SAH100 Tablets original NDA. Does the Division have any concerns with this approach?

**Preliminary Response:** We do not have any concerns with this approach.

11. Does the Division agree with the proposed biowaiver strategy in Section 4.2 for the originally proposed dose strengths of 150/5/12.5 mg, 300/5/12.5 mg and also for the additional 300/10/12.5 mg dose strength of SAH100?

**Preliminary Response:** Please refer to the response to question 5.

**General**

12. Does the Division have any other comments on our proposal?

**CMC**

It is not clear that the Identity Test is based solely on retention time or combined with UV. The Identity Test should be specific, e.g. infra-red spectroscopy or a combination of tests into a single procedure, such as HPLC/UV diode array.

Meeting recorder: \_\_\_\_\_  
John David

Meeting concurrence: \_\_\_\_\_  
Norman Stockbridge, M.D., Ph.D.

Draft: jd/2-26-09

Final: jd/3-9-09

RD:

Shiromani 3/4/09

Srinivasachar 3/4/09

Xiao 2/26/09

Marciniak 2/27/09

Kumi 3/5/09

Marroum 3/6/09

Stockbridge 3/9/09

Linked Applications

Sponsor Name

Drug Name / Subject

IND 101386

NOVARTIS  
PHARMACEUTICALS  
CORP

ALISKIREN/AMLODIPINE/HCTZ TABLETS

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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.**  
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/s/  
-----

NORMAN L STOCKBRIDGE  
03/09/2009

**DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
CDER, DCRDP (HFD-110)  
10903 New Hampshire Ave.,  
Silver Spring, MD 20993-0002

FDA  
10903 New Hampshire Ave  
Silver Spring, MD 20993-00025600

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**Transmitted via email to:** kimberly.dickerson@novartis.com  
**Attention:** Kimberly Dickerson  
**Company Name:** Novartis Pharmaceutical Corporation  
**Phone:** 862-778-4576  
**Subject:** IND 101,386 March 14 2008 PIND TCON Minutes  
**Date:**

**Pages including this sheet:**

**From:** CDR John David  
**Phone:** 301-796-1059  
**Fax:** 301-796-9838

**\*\*\*\*\*PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Minutes of a Tcon between Novartis Pharmaceutical Corporation and the FDA Division of Cardiovascular and Renal Products

Sponsor: Novartis Pharmaceutical Corporation  
Drug: Aliskiren/Amlodipine/Hydrochlorothiazide  
BB IND: 101,386  
Date of request: January 17, 2008  
Date request received: January 25, 2008  
Date of confirmation: January 30, 2008  
Date of pre-meeting: March 4, 2008  
Date of meeting: March 14, 2008  
Time: 9-9:30 am

Type/Classification: B/Pre-IND

Meeting Chair: Norman Stockbridge

Meeting recorder: John David

FDA Participants:

Norman Stockbridge, M.D., Ph.D. Director, Division of Cardio-Renal Drug Products, HFD-110  
Thomas Marciniak, M.D. Team Leader, Medical Officer, HFD-110  
Elena Mishina, Pharm. D Clinical Pharmacology, HFD-860  
Alison Blas Regulatory Health Project Manager, HFD-110  
John David Regulatory Health Project Manager, HFD-110

Novartis Pharmaceuticals Corporation Participants:

Adrian Birch Vice President, Drug Regulatory Affairs  
Kimberly Dickerson, Pharm.D. Associate Director, Drug Regulatory Affairs  
Marjorie Gatlin, M.D. Vice President, CVM TA Head, US Medical  
Huang Hsu, Ph.D. Associate Director, Biostatistics  
Venkateswar Jarugula, Ph.D. CVM, TA Head, ED-DMPK Pharmacokinetics  
Olga Santiago Global Program Director for Aliskiren Development Projects  
Suliman Al-fayoum, Ph.D. ED-DMPK Pharmacokinetics  
Jack Zhang, M.D. Sr. Director, Global Clinical Development & Medical Affairs

Background:

Novartis plans to sponsor clinical trials using a fixed-dose combination of aliskiren (Tekturna), amlodipine, and hydrochlorothiazide (HCTZ) in patients with hypertension. Novartis indicated that this therapeutic alternative to free combinations of multiple drugs could possibly offer an advantage of convenience, by reducing the number of dosage forms and simplifying the treatment regimen, and hence the potential for improved patient compliance, better BP control, and outcomes. The most likely candidates for the proposed combination therapy are patients whose blood pressure is inadequately controlled by aliskiren (or another DRI)/HCTZ or amlodipine (or another CCB)/HCTZ, or aliskiren (or another DRI)/amlodipine (or another CCB), or those patient who need three agents to achieve the recommended blood pressure.

The purpose of this meeting is to describe the clinical development plan, biopharmaceutics development plan, preclinical safety development plan, and technical development plan for the fixed-dose combination of aliskiren (Tekturna), amlodipine, and hydrochlorothiazide (HCTZ).

**Questions for the Division:**

1. The proposed clinical development plan (i.e., CSPA100A2301, CSPP100A2344, CSAH100A2301, and CSAH100A2302) to support the registration of fixed combinations of aliskiren/amlodipine/hydrochlorothiazide fixed-combination has been outlined. Does the Division agree with the clinical study program to support a treatment of essential hypertension filing for aliskiren/amlodipine/hydrochlorothiazide fixed-combination at the doses envisioned?

**Preliminary Response:** Yes, but see also our comments in our responses to the following questions.

**Discussion during Tcon:** There was no further discussion regarding this question.

2. Does the Division agree that the proposed study design, patient selection (Stage 2 hypertensive patients based on either DBP or SBP), and the use of systolic blood pressure reduction as the primary efficacy endpoint in pivotal Study CSAH100A2302 will support the registration of the triple fixed combination?

**Preliminary Response:** Yes, but we have the following comments:

- a. We recommend that the BP measurements used for baseline be different from those used for eligibility to avoid regression-to-the-mean effects.
- b. The triple combination must beat the double combinations by a clinically meaningful difference, i.e., 2 mm Hg.
- c. You must also show the effects of the combinations upon BP control throughout the interdosing interval. We suggest you provide such demonstration within an ABPM substudy.

**Novartis's Response received March 13, 2008:** There was no further discussion regarding question 2b and 2c. Regarding 2a Novartis indicated that they have given this recommendation careful consideration and acknowledges that the rationale for this recommendation is one of the ways to minimize the "placebo" effect. There are inherent logistical issues with incorporating an additional measurement for baseline BP; therefore, we have considered other methodologies to reasonably minimize the "placebo" effect, such as use of an automated blood pressure monitor, increasing the quiet resting time for patients, defining a specific procedure for BP measurement, and providing investigator training for consistency.

**Discussion during Tcon:** Dr. Stockbridge agreed with the sponsor's proposal regarding 2a.

3. It is estimated that a total of 800 patients from Studies CSAH100A2301, CSAH100A2302, CSPA100A2301 and CSPP100A2344 will be exposed to the triple combination treatment of aliskiren/amlodipine/HCTZ with at least 300 patients treated with the highest dose for at least 6 months. Does FDA agree that the proposed safety database is of adequate scope (number and duration of patient exposures, and number of exposures at each dose) for registration? An analysis is planned for Study CSAH100A2301 when at least 300 patients complete the 28 weeks of treatment (6 month highest dose). We propose to use the data from this analysis as the long-term safety data for the NDA submission. Does the FDA agree that the design of the long term open label study CSAH100A2301 using 6-month cohort data will be appropriate to support registration?

**Preliminary Response:** Yes.

**Discussion during Tcon:** There was no further discussion regarding this question.

4. The primary objective of the core efficacy trial (CSAH100A2302) is to demonstrate that aliskiren, amlodipine, and hydrochlorothiazide contribute to the efficacy of the combination. Does the Division have any comments on the statistical methods planned within this study?

**Preliminary Response:** The primary analysis is acceptable. Note that the placebo effect cannot be estimated from this trial.

**Discussion during Tcon:** There was no further discussion regarding this question.

5. Does FDA agree that the use of a population PK approach to characterize the drug-drug interaction potential is acceptable to support the registration of the aliskiren/amlodipine/hydrochlorothiazide fixed-combination?

**Preliminary Response:** Yes, a population PK approach to characterize the drug-drug interaction potential is acceptable. However, your proposed study does not include the arms with monotherapies for each of the components. Drug-drug interactions should be assessed by comparing the pharmacokinetics of each drug monotherapy to the triple drug combination.

**Novartis's Response received March 13, 2008:** Previous studies have demonstrated the lack of clinically meaningful drug-drug interactions between the dual components (aliskiren/HCTZ and aliskiren/amlodipine). Novartis believes that a drug-drug interaction (DDI) evaluation comparing the triple combination to the double combinations is appropriate to supplement the clinical results. The pivotal clinical study (SAH100A2302) was designed to compare the triple combination to the double combinations. The drug-drug interaction evaluation was therefore designed to facilitate the interpretation of the clinical study results and provide meaningful information to health care professionals that are considering the triple combination for patients who are already on the double combinations.

**Discussion during Tcon:** Dr. Stockbridge noted the variability of the 2-drug combination would need to be taken into account in evaluating the 3-drug vs. 2-drug comparisons. He reiterated that drug-drug interactions of interest were comparing the pharmacokinetics of each drug monotherapy to the triple drug combination, but he would consider any arguments or proposal submitted by the sponsor.

6. Does FDA agree that the biopharmaceutics/clinical pharmacology program is adequate to support registration of the aliskiren/amlodipine/hydrochlorothiazide fixed-combination? Does FDA agree with the planned biowaiver strategy?

**Preliminary Response:** Yes.

**Discussion during Tcon:** There was no further discussion regarding this question.

7. Does FDA agree that the completed preclinical studies will be adequate to support registration of the aliskiren/amlodipine/hydrochlorothiazide fixed-combination?

**Preliminary Response:** Yes.

**Discussion during Tcon:** There was no further discussion regarding this question.

8. Proposed labeling text is included in the briefing documents. Does FDA agree that the proposed data package of previous, ongoing, and proposed studies, if successful, would support approval of our desired labeling statements?

**Preliminary Response:** Your proposed data package does not support switching from the monotherapies directly to the triple combination. It also does not support switching from combinations including any calcium channel blocker or any direct renin inhibitor to the triple combination. You would have to augment

your proposed data package and studies to support the latter two labeling statements. The final labeling text, of course, will reflect only what your submitted data package supports.

**Discussion during Tcon:** There was no further discussion regarding this question.

9. The pivotal trial for this clinical program utilizes free-combination tablets; however, Novartis has an interest in obtaining the Division's perspective if the final market image (FMI) was utilized. Does the FDA agree that if the pivotal trial is conducted using the FMI that this study in conjunction with the other supportive phase 2 and 3 trials as outlined would support the registration of aliskiren/amlodipine/hydrochlorothiazide fixed-combination tablets for an add-on indication in antihypertensive therapy? This would not depend on bioequivalence data.

**Preliminary Response:** Yes.

**Discussion during Tcon:** There was no further discussion regarding this question.

10. Is the Division in agreement with our request for a waiver of the pediatric requirement?

**Preliminary Response:** Your request for a waiver will be reviewed by the Pediatric Review Committee (PeRC) once your NDA is submitted.

**Discussion during Tcon:** There was no further discussion regarding this question.

Meeting recorder: \_\_\_\_\_  
John David

Meeting concurrence: \_\_\_\_\_  
Norman Stockbridge, M.D., Ph.D.

Draft: jd/3-14-08

Final: jd/3-21-08

RD:

Mishina 3/14/2008

Marciniak 3/21/08

Stockbridge 3/21/08

Linked Applications

Sponsor Name

Drug Name

IND 101386

Novartis

(b) (4)

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

/s/

NORMAN L STOCKBRIDGE

03/21/2008

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	see attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Deborah Keefe, MD, MPH	TITLE Global Brand Medical Director, Aliskiren
FIRM/ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE 	DATE (mm/dd/yyyy) 12/15/2009

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
1350 Piccard Drive, 420A  
Rockville, MD 20850

# DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning \_\_\_\_\_ (b) (4), who participated  
Name of clinical investigator  
as a clinical investigator in the submitted study \_\_\_\_\_ (b) (4)  
Name of  
\_\_\_\_\_ is submitted in accordance with 21 CFR part 54. The  
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Deborah Keefe, M.D.	TITLE Global Program Medical Director, Aliskiren
FIRM/ORGANIZATION Novartis Pharmaceuticals	
SIGNATURE <i>Deborah Keefe MD</i>	DATE <i>Oct 5, 2009</i>

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

## DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

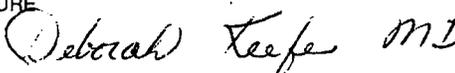
The following information concerning \_\_\_\_\_ (b) (4), who participated  
Name of clinical investigator  
as a clinical investigator in the submitted study \_\_\_\_\_ (b) (4)  
Name of

\_\_\_\_\_ is submitted in accordance with 21 CFR part 54. The  
clinical study  
named individual has participated in financial arrangements or holds financial interests that are  
required to be disclosed as follows:

Please mark the applicable check boxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Deborah Keefe, M.D.	TITLE Global Program Medical Director, Aliskiren
FIRM/ORGANIZATION Novartis Pharmaceuticals	
SIGNATURE 	DATE Oct. 5, 2009

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

**PRESCRIPTION DRUG USER FEE  
COVERSHEET**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website:

<http://www.fda.gov/forindustry/userfeeuserfee/PrescriptionDrugUserFee/default.htm>

<p><b>1. APPLICANT'S NAME AND ADDRESS</b></p> <p>NOVARTIS PHARMACEUTICALS CORP Lina Thomas One Health Plaza East Hanover NJ 07936 US</p>	<p><b>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER</b></p> <p>200-045</p>
<p><b>2. TELEPHONE NUMBER</b></p> <p>862-778 2488</p>	<p><b>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?</b></p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:</p>

<p><b>3. PRODUCT NAME</b></p> <p>(b) (4) ( Aliskiren/Amlodipine/Hydrochlorothiazide )</p>	<p><b>6. USER FEE I.D. NUMBER</b></p> <p>PD3010135</p>
---	--

**7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.**

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

**8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?**  YES  NO

**OMB Statement:**  
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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<p><b>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</b></p> 	<p><b>TITLE</b></p> <p>SVP, DRA</p>	<p><b>DATE</b></p> <p>2/15/2010</p>
--	-------------------------------------	-------------------------------------

**9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION**  
\$1,405,500.00