

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-314

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

NDA 22-314

Patent Information -

See EDR submission at

<\\CDSESUB1\EVSPROD\NDA022314\022314.enx>

EXCLUSIVITY SUMMARY

NDA # 22-314

SUPPL #

HFD # 110

Trade Name Exforge HCT Tablets

Generic Name amlodipine, valsartan, hydrochlorothiazide

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known 4/30/09

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# 19-787 Norvasc (amlodipine besylate) Tablets

NDA# 20-665 and 21-283 Diovan (valsartan) Capsules and Diovan (valsartan) Tablets

NDA# 11-793 Esidrix (hydrochlorothiazide) Tablets

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:

Study VEA A2302

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"):

Study VEA A2302

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 # 74,490 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

Explain:

!

!

! NO

! 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: Quynh Nguyen, Pharm.D.
Title: Regulatory Health Project Manager, Division of Cardiovascular and Renal Products
Date: 4/30/09

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

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

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

/s/

Ellis Unger
4/30/2009 09:36:22 AM
for Norman Stockbridge, M.D., Ph.D.

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-314 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Cardiovascular and Renal Products PDUFA Goal Date: 4/30/09 Stamp Date: 6/30/08

Proprietary Name: Exforge HCT

Established/Generic Name: amlodipine besylate, valsartan, hydrochlorothiazide

Dosage Form: Tablet

Applicant/Sponsor: Novartis Pharmaceuticals Corporation

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of hypertension.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
 Disease/condition does not exist in children
 Too few children with disease/condition to study
 Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

Pediatric Research and Equity Act Waivers

IND/NDA/BLA #: 22-314

Supplement Type: ____

Supplement Number: ____

Product name and active ingredient/dosage form: Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) Tablets

Sponsor: Novartis Pharmaceuticals Corporation

Indications(s): Treatment of hypertension.

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth to 16 years old
2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

Justification: Exforge HCT is a combination antihypertensive agent. There are single agent products studied and labeled for use in pediatrics, and most pediatric patients are not treated with combination antihypertensives (supported by **The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**, *Pediatrics* 2004;114:555-576).

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

/s/

Quynh Nguyen
4/23/2009 12:16:57 PM



NDA No. 22-314

Exforge®HCT (amlodipine besylate and valsartan and
hydrochlorothiazide)
Tablets
New Drug Application

**NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992**

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.

Donna Vivalo

Donna Vivalo
Executive Director
Drug Regulatory Affairs

5/12/2008

May 12, 2008



DIVISION OF CARDIOVASCULAR AND RENAL DRUG PRODUCTS
Memorandum

NDA Number: 22314
Document Type: Financial Disclosure

Name of Drug: Exforge HCT
Formulation: valsartan/amlodipine/hydrochlorothiazide
Proposed Indication: treatment of hypertension
Sponsor: Novartis

Date: April 7, 2009
Reviewer: Shona Pendse, MD, MSc

The sponsor provided a FDA Form 3454 financial disclosure certification for the investigators in Study VEA489A2302, the pivotal efficacy study, as well as all of the supporting studies. Response rates were 100% in all studies except for Study 489A2302, the pivotal study, which had a response rate of 99.6% for the US centers (2 centers out of a total of 521 US centers did not respond).

Of the returned forms, only one identified a financial interest. This was an investigator from Study _____, who reported "Honoraria and travel expenses for education activities" exceeding \$25,000.

Reviewing the remainder of the financial disclosure information, we found that all of the investigators from all of the centers in Slovakia reported having financial interest. When we emailed the sponsor inquiring as to the nature of this financial interest, they replied with the statement that none of these Slovakian investigators were in the pivotal efficacy study, but were only involved in Study VAA489A2401, one of the supporting studies.

Bias was minimized, however, with the use of multiple countries/study sites and investigators, by the independent data monitoring by Novartis, and by the use of the randomized, double-blind, active-controlled design.

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/

Shona Pendse
4/9/2009 07:42:33 AM
MEDICAL OFFICER

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 22-314 SUPP TYPE & # N-000 Division 110 UFID # PD3008445
 Applicant Name: NOVARTIS PHARM Drug Name: EXFORICE HCT

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?
 Yes No

 2. Firm in Arrears?
 Yes No

 3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees"
<http://www.fda.gov/cder/guidance>
 Yes No (explain in comments)

 4. Administrative Split? (list all NDA#s and Divisions)

NDA #/Doc Type	Div.	Fee? (Y/N)
<u>na</u>		

 5. Type 6?
 Yes No
 Type 6 to which other application?
 NDA # _____ Supp Type & # _____

 6. Clinical Data Required for Approval? (Check one)
 Yes*
 Yes, by reference to another application
 NDA # _____ Supp Type & # _____
 No
- * Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)"
<http://www.fda.gov/cder/guidance>
 Yes No To be determined

8. Subpart H (Accelerated Approval/Restricted Distribution)?
 Yes No To be determined

9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)
List of exclusions:
 2 - No fee - administrative split
 4 - No fee - 505b2
 7 - Supplement fee - administrative split
 9 - No fee Subpart H supplement - confirmatory study
 11 - No fee Orphan Exception
 13 - No fee State/Federal exemption from fees

10. Waiver Granted?
 Yes (letter enclosed) No
Select Waiver Type below: Letter Date: _____
 Small Business Barrier-to-Innovation
 Public Health Other (explain)

11. If required, was the appropriate fee paid?
 Yes No

12. Application Review Priority
 Priority Standard To be determined

13. Fast Track/Rolling Review Presubmission?
 Yes No

Comments

[Signature] 7/11/08
 PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

CC: original archival file
 10-0-007

Processor Name & Date

QC Name & Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

This 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/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS NOVARTIS PHARMACEUTICALS CORP Lina Thomas One Health Plaza East Hanover NJ 07936 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 22-314
2. TELEPHONE NUMBER 862-778 2488	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO 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: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME Exforge HCT(R) (Amlodipine, valsartan and hydrochlorothiazide)	6. USER FEE I.D. NUMBER PD3008445
--	---

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.
--	--	--

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>M. M. Shelton</i>	TITLE Sr. VP DRA	DATE June 12, 2008
---	--------------------------------	----------------------------------

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$1,178,000.00

NDA No. 22-314**VEA489 (Exforge HCT®)****(amlodipine besylate/valsartan/hydrochlorothiazide)****5/160/12.5mg; 10/160/12.5mg; 5/160/25mg; 10/160/25mg;
10/320/25mg****Tablets****Field Copy Certification Statement 21 CFR 314.50(k)(3)**

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.

Name: Nancy Landzert Date: 30-Jun-2008
Signature: *Nancy Landzert*
Title: Associate Director
Department: Global Regulatory CMC

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-314	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Exforge HCT Established Name: amlodipine, valsartan, hydrochlorothiazide Dosage Form: Tablets		Applicant: Novartis Pharmaceuticals Corporation
RPM: Quynh Nguyen, Pharm.D., RAC		Division: DCRP Phone # 301-796-0510
NDAs: 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) (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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 19-787 Norvasc (amlodipine beyslate) Tablets Provide a brief explanation of how this product is different from the listed drug. Exforge HCT is a combination product of amlodipine, valsartan, and hydrochlorothiazide tablets. <input type="checkbox"/> If no listed drug, check here and explain: Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct. <input type="checkbox"/> Confirmed <input checked="" type="checkbox"/> Corrected Date: 4-28-09
❖ User Fee Goal Date		4-30-09
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(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 to the next section below (Summary Reviews).

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).

- (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?

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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>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 Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) <i>(indicate date for each review)</i>	Division Director's Memo, 4-25-09
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) <i>(indicate date)</i>	
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Included
❖ Patient Package Insert	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	Included
❖ Medication Guide	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
❖ Labeling reviews and minutes of any labeling meetings <i>(indicate dates of reviews and meetings)</i>	<input checked="" type="checkbox"/> DMETS 2-27-09; 4-17-09 <input checked="" type="checkbox"/> DSRCS 4-7-09 <input checked="" type="checkbox"/> DDMAC 3-31-09; 3-2-09 <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	9-10-08; 4-29-09
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ 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>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	<input checked="" type="checkbox"/> None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	N/A
	<input type="checkbox"/> No mtg 5-15-07
	<input checked="" type="checkbox"/> No mtg
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	<input checked="" type="checkbox"/> No AC meeting
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	4-20-09; 3-3-09
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-7-09; 2-2-09
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> <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>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	3-4-09; 3-5-09
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 4-7-09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	11-6-08
❖ 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	
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	4-23-09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	4-9-09
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	4-9-09
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	
• Bioequivalence Studies	4-14-09
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-23-09
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2-27-09

Appendix A 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 Office of Regulatory Policy representative.

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/s/

Quynh Nguyen .
4/30/2009 09:41:28 AM

clinical portion of study# VEA489A2305 was conducted at _____
The
clinical portion of study# VEA489A2306 was conducted at _____
Following the inspection of _____
(November 12-18, 2008), _____(January 7-12, 2009), and _____
(March 23-27, 2009), Form FDA 483 was not issued.
However, there were discussion items at all 3 inspections.
Three of the discussion items at _____ are discussed
below. The remaining discussion items at _____
_____ do not have significant impact on study
outcomes.

b(4)

b(4)

Clinical Site for Study VEA489A2305 - _____

1. Twenty-two PK samples, of the data reviewed for seven subjects (subject 5101, 5102, 5103, 5104, 5105, 5113 and 5122), were not centrifuged within 15 minutes of collection as required by the protocol. These 22 PK samples were centrifuged between 16 and 37 minutes after sample collection.

Subject	Period	Sample Collection Time Point (Hours)	Period of Time Between Sample Collection and Centrifuging (Minutes)
5101	1	144	17
5101	2	0.5	16
5101	2	24	26
5101	2	48	18
5101	2	120	33
5101	2	144	18
5101	3	8	16
5101	4	36	23
5101	4	120	16
5102	2	48	21
5102	2	120	28
5103	2	120	23
5103	4	3	19
5104	2	120	18
5104	4	2	37
5105	2	96	19
5113	1	8	21
5113	2	0.5	16
5113	2	10	18
5113	3	168	20
5122	1	72	16
5122	1	168	24

The protocol required blood samples to be centrifuged within 15 minutes of the blood draw. Since these samples were centrifuged up to 22 minutes late, the firm should provide stability data to demonstrate the stability of the analyte concentrations under these conditions.

2. There is no documentation of the time of centrifuging for the following three PK samples:

Subject	Period	Sample Collection Time Point (Hours)
5101	2	8
5102	2	8
5103	2	8

Because the centrifugation time was not recorded for these samples, the integrity of these three samples cannot be assured.

3. There is no documentation of the time that the following eight PK samples were put in the freezer:

Subject	Period	Sample Collection Time Point (Hours)
5111	2	12
5113	1	12
5114	1	12
5115	1	12
5116	1	12
5129	1	12
5130	1	12
5131	1	12

There was no record to verify that the listed samples were frozen immediately after centrifuging as required by the protocol. Therefore, the integrity of these 8 samples cannot be assured.

Conclusion:

DSI recommends data from Study VEA489A2306 be accepted for review. For Study VEA489A2305, DSI recommends the following:

- The firm should provide stability data to demonstrate analyte stability for the processing conditions mentioned in item #1. If the sample integrity question is not resolved, DSI is of the opinion that data from these samples should be excluded from bioequivalence determination.
- Data from the 11 samples mentioned in items #2 and #3 should be excluded from bioequivalence determination.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Martin K. Yau

Martin K. Yau, Ph.D.

Samuel H. Chan

Samuel H. Chan, Pharm.D.

Final Classifications:

VAI - _____
NAI - _____
NAI - _____

b(4)

cc: DFS
DSI/RF
DSI/Viswanathan/Yau/Chan
DSI/Patague/Rivera-Lopez/CF
DCRP/Stockbridge/Nguyen
OCP/Menon-Anderson/Dorantes/Kumi, R
cc: email
HFR-SW1575/Robert Lorenz (BIMO)
HFR-SW1540/Joel Martinez (BIMO)
HFR-CE250/Shapley (BIMO)
HFR-CE3565/Marciante (BIMO)
Draft: SHC 4/2/09
Edit: MKY 4/10/09 MFS 4/13/09
DSI: _____ O:\BE\eircover\22314nov.exf.doc
FACTS: _____

b(4)

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/s/

Samuel Chan
4/14/2009 11:31:36 AM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-314

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corp.
Attention: Catherine Ford
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Ford:

Please refer to your June 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) tablets.

We also refer to your submissions dated March 3, 2009 and March 6, 2009.

We are reviewing the Chemistry, Manufacturing and Controls section 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 in this NDA review cycle the updated Exforge HCT tablet testing monographs that incorporates tightening of the limit of total impurities from NMT ~~to~~ \geq NMT ~~and~~ revision of the limit of ~~to~~ content to NMT ~~to~~
2. Submit individual tablet dissolution data used to generate plots for Figure 12-1 and Figure 12-2 provided in your response to Question 12 of the Amendment dated March 6, 2009.

b(4)

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 Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
3/25/2009 03:05:34 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-314

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corp.
Attention: Agata Slopianka, PhD, CMC Project Team Leader
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Slopianka:

Please refer to your June 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) tablets.

We also refer to your submission dated November 21, 2008.

We are reviewing the Chemistry, Manufacturing and Controls section 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. Based on the results of the release and stability data for all drug product batches, we recommend the following revision to the drug product dissolution specification. Provide updated drug product specifications according to this revision:
 - The Q-value for amlodipine should be \rightarrow release of amlodipine in 30 minutes for 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg strengths tablets.
 - The Q-value for amlodipine should be \leftarrow release of amlodipine in 30 minutes for 10/320/25 mg strength tablets.

b(4)

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 Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
2/4/2009 04:05:41 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-314

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corp.
Attention: Nancy Price
Executive Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Price:

Please refer to your June 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section 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 data demonstrating how the blend uniformity is assured during the manufacturing process of the Exforge HCT film-coated tablets.
2. Since two methods used for determination of Assay and Degradation Products (one with manual sample preparations and another one, robotic method) demonstrated discrepancy for determination of valsartan, clarify which method was used for assay determinations in the submitted data (e.g., stability batches, batch analysis etc.) and which method will be used for all future determinations.
3. Provide information whether the manufactured drug product batches of all strengths are representative of drug substance batches from all three sources (manufacturers) of amlodipine besylate.
- 4.
- 5.
- 6.
7. J
8. Explain why the HOW SUPPLIED/STORAGE AND HANDLING section of the package Insert lists only — bottles of 30 and 90 counts tablets with no mention of 100 count bottles or blister packaging. Include the missing information in the Package Insert, if necessary.
9. Explain why carton and bottle labeling for — bottles of 100 counts and — is not provided. Provide the missing information.
10. Provide carton labels for — bottles and blisters if applicable.
11. Change the chemical name used for amlodipine besylate in Description Section to the following USAN name, 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(*o*-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate.

b(4)

b(4)

b(4)

b(4)

b(4)

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 Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
1/23/2009 03:13:30 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-314

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy A. Price
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your June 30, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exforge HCT (amlodipine, valsartan, hydrochlorothiazide) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section 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. The _____ DMF # _____ which you are referencing for drug substance Amlodipine Besylate, is currently inadequate. A deficiency letter was sent to the DMF holder. In order to have an approval of your submitted NDA, the DMF # _____ must receive an adequate status. b(4)
2. Include a limit for the _____ of NMT _____ in the amlodipine besylate drug substance specification [refer to the Test Specification (Test 30001.01) "Impurities by HPLC" of the Novartis's Test Specification for Amlodipine Besylate from _____]. b(4)

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 Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
11/24/2008 11:53:41 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-314

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy A. Price
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your new drug application (NDA) dated June 30, 2008 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Exforge HCT (amlodipine USP, valsartan USP, hydrochlorothiazide USP) 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 10/320/25 mg Tablets.

We also refer to your submissions dated August 12 and 25 (two), 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is April 30, 2009.

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

1. According to the agreement during the teleconference held on December 12, 2007, provide the dissolution data at 10, 15, 20 and 30 minutes obtained during the stability studies on primary drug product batches by the mid-cycle of the review time, i.e., November 30, 2008.
2. Provide updated shelf life stability data for the drug product up to 12 months or longer not later than by the mid-cycle of the review time, i.e., November 30, 2008. Refer to the ICH guidance Q1A (R2).
3. Please submit the programs for the analyses of primary and secondary endpoints for the pivotal efficacy study.

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

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for all pediatric patients.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 9, 2009.

If you have any questions, please call:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

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

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/s/

Norman Stockbridge
9/15/2008 08:49:43 AM

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-314 BLA#	NDA Supplement #: BLA STN #	Efficacy Supplement Type:
Proprietary Name: Exforge HCT Established/Proper Name: amlodipine USP, valsartan USP, hydrochlorothiazide USP Dosage Form: Tablet Strengths: 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 10/320/25 mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: 6/30/08 Date of Receipt: 6/30/08 Date clock started after UN:		
PDUFA Goal Date: 4/30/09	Action Goal Date (if different):	
Filing Date: 8/29/08 Date of Filing Meeting: 8/22/08		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed Indication(s): Treatment of hypertension.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		
Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 74,490	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aiplist.html	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If yes, explain:	
If yes, has OC/DMPQ been notified of the submission?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
Comments: User Fee ID Number PD3008445	
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? Check the <i>Electronic Orange Book</i> at: http://www.fda.gov/cder/ob/default.htm	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? <i>(NDAs/NDA efficacy supplements only)</i></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<p><input type="checkbox"/> YES # years requested: <input checked="" type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use <i>(NDAs only)</i>:</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p>Format and Content</p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If not, explain (e.g., waiver granted):</p>			

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments: Listed in attachment and amendments</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
<p><u>PREA</u></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • <i>If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</i> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments: Consult request to SEALD, OSE, and DDMAC sent on 8/18/08.	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: Consult request sent on 8/18/08.	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: Consult request sent on 8/18/08.	
REMS consulted to OSE/DRISK?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: Consult request sent on 8/18/08.	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): 12/12/07 CMC Telecon <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): 5/9/07 (Pre-NDA); 10/13/04 (Guidance) <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): 11/3/05 <input type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8/22/08

NDA/BLA #: 22-314

PROPRIETARY/ESTABLISHED NAMES: Exforge HCT (amlodipine USP, valsartan USP, hydrochlorothiazide, USP) Tablets

APPLICANT: Novartis Pharmaceuticals Corporation

BACKGROUND: This original NDA provides for the use of Exforge HCT Tablets for the treatment of hypertension. The NDA was submitted pursuant to section 505(b)(2) and contains full study reports of the safety and efficacy of the combination drug product. However, reference is made to certain information previously submitted to the Agency for Norvasc (amlodipine besylate) for the preclinical data. The sponsor has submitted a paragraph II certification.

In support of approval, the submission includes quality, pre-clinical, clinical pharmacology, and clinical/statistical data. The clinical development program included 10 clinical studies (including one pivotal Phase 3 study and other supportive studies), bioequivalence studies, a food effect study, and a pharmacokinetic drug-drug interaction study. The following dosage strengths of amlodipine/valsartan/HCTZ are being proposed: 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 10/320/25 mg.

The sponsor submitted an Environmental Assessment (EA) and an EA consult has been sent to OPS. Manufacturing, testing, and packaging facilities have been entered into EES. The sponsor is requesting a biowaiver for the following dose strengths: 10/160/12.5, 5/160/25, and 10/320/25 mg of amlodipine/valsartan/HCTZ.

The pivotal trial (Study VEA489A2302) was an 8-week, multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of the triple combination compared to the dual combinations in patients with moderate to severe hypertension. A two-week forced-titration was used to achieve maximum once-daily doses of the triple combination amlodipine/valsartan/HCTZ 10/320/25 mg, valsartan/HCTZ 320/25 mg, valsartan/amlodipine 320/10 mg, and HCTZ/amlodipine 25/10 mg, which continued for an additional 6 weeks. A total of 2,271 patients were randomized and 2,060 patients completed the study. According to the sponsor, the triple combination produced clinically and statistically significant greater reductions in MSDBP and MSSBP compared to the dual combinations, and no new or unexpected safety issues were identified with triple therapy compared to any of the dual therapies.

Draft labeling for the carton and container, PI, and Patient PI was submitted in SPL and PLR format. Consult requests were sent to DDMAC, OSE, and SEALD on 8/18/08 for review of the proposed labeling.

The sponsor is requesting a waiver from the pediatric requirement, as discussed during the May 9, 2007 Pre-NDA meeting. During the Filing Meeting, the Division agreed that a pediatric waiver should be granted because the drug product is a combination antihypertensive drug.

The NDA is fully electronic in e-CTD format.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Quynh Nguyen	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Stephen Grant		Y
Clinical	Reviewer:	Salma Lemtouni	Y
	TL: acting	Stephen Grant	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OSE	Reviewer:	DMEPA: Walter Fava DRISK: Sharon Mills DPV: Monika Houstoun	N
	TL:	DMEPA: Linda Kim-Jung DRISK: Jodi Duckhorn DPV: Cindy Kortepeter	N
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Divya Menon-Andersen	Y
	TL: acting	Robert Kumi	Y
Biostatistics	Reviewer:	Ququan (Cherry) Liu	Y
	TL:	James Hung	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gowra Jagadeesh	Y
	TL:	Charles Resnick	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Lyudmila Soldatova	Y
	TL:	Kasturi Srinivasachar	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Norman Stockbridge, Sean Bradley, Phillip Gati

505(b)(2) filing issues?	<input type="checkbox"/> Not Applicable
If yes, list issues:	<input type="checkbox"/> YES
	<input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?	<input checked="" type="checkbox"/> YES
If no, explain:	<input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: A joint clinical and statistical review will be done.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: The medical officer and statistician agreed that a DSI inspection of the pivotal study was not needed. Per Dr. Lemtouni, half the population comes from the US and the effect is highly significant in the US. The site of concern (Russia) was less than 10% of the overall population. Argentina enrolled about 15%. These two countries, because of their small numbers, are unlikely to be driving the findings. Per Dr. Liu, after excluding Russia and Argentina, the overall efficacy remains the same; the triple combination of valsartan/HCTZ/amlodipine was statistically superior to the dual combinations ($p < 0.0001$).</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p>If no, for an original NME or BLA application, include the reason. For example:</p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: A joint clinical and statistical review will be done.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>• Establishment(s) ready for inspection?</p> <p>▪ Establishment Evaluation Request (EER/TBP-EER)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable

submitted to DMPQ?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
• Sterile product?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)	<input type="checkbox"/> YES <input type="checkbox"/> NO
FACILITY (BLAs only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division	
GRMP Timeline Milestones: Team meetings to be scheduled (1/month, as needed). Mid-cycle Meeting scheduled for 12/2/08.	
Comments: Expected completion date for all primary reviews is February 28, 2009.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

/s/

Quynh Nguyen
9/10/2008 01:59:53 PM
CSO

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-314	NDA Supplement #	Efficacy Supplement Type
Proprietary Name: Exforge HCT Established/Proper Name: amlodipine USP, valsartan USP, hydrochlorothiazide USP Dosage Form: Tablet Strengths: 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 10/320/25 mg		
Applicant: Novartis Pharmaceuticals Corporation		
Date of Receipt: 6/30/08		
PDUFA Goal Date: 4/30/09		Action Goal Date (if different):
Proposed Indication(s): Treatment of hypertension.		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "YES," proceed to question #3.

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Norvasc (amlodipine besylate) Tablet NDA 19-787	Preclinical data

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
BA/BE studies

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #6.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #6

If "YES", list the listed drug(s) identified by name and answer question #5(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application rely on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
- YES NO

If "NO," proceed to question #11.

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Norvasc (amlodipine besylate) Tablet	NDA 19-787	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
- YES NO

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

9. Were any of the listed drug(s) relied upon for this application:

- a. Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b. Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c. Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d.1.

If "NO", proceed to question #10.

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution"). This application provides for a new dosage form (fixed combination product of valsartan amlodipine, and hydrochlorothiazide).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO," to (a) proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "YES" and there are no additional pharmaceutical equivalents listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #13.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #13.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

13. List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): N/A – For Norvasc (amlodipine besylate), there are no unexpired patents in the Orange Book Database.

14. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

15. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

YES NO

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

YES NO

- Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

Patent number(s):

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

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/s/

Quynh Nguyen
9/10/2008 02:02:01 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-314

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Nancy A. Price
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Price:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Exforge HCT[®] (amlodipine besylate USP, valsartan USP, hydrochlorothiazide USP) Combination Tablets

Date of Application: June 30, 2008

Date of Receipt: June 30, 2008

Our Reference Number: NDA 22-314

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 30, 2008 in accordance with 21 CFR 314.101(a).

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the

certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Amundson Road
Beltsville, MD 20705-1266

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

If you have any questions, please contact:

Ms. Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
7/25/2008 02:50:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,174

Novartis Pharmaceuticals Corporation
Attention: Ms. Donna Vivelo
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Vivelo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VAA489A (valsartan/amlodipine) Capsules.

We also refer to your amendment dated March 13, 2008 (serial number 084), containing your new protocol, Study No. CVAA489AUS02, entitled "A multicenter, randomized, double blind parallel design trial to evaluate the blood pressure lowering efficacy comparing moderate versus aggressive treatment regimen of Exforge in patients uncontrolled on ARB monotherapy."

We have the following comments and requests for additional information. Please note that these requests are not clinical hold issues; however, response to them is requested:

1. Please clarify whether or not Last Observation Carried Forward (LOCF) will be used to handle missing data for the primary efficacy analysis.
2. In Section 10.4.3, you state that "longitudinal fit of the data" will be another method used to handle missing data. Please provide details of the method for "longitudinal fit of the data."
3. Please submit the Statistical Analysis Plan (SAP) to the Agency well in advance of significant enrollment.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

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

Linked Applications

Sponsor Name

Drug Name

IND 65174

NOVARTIS PHARMA AG

DIOVAN/NORVASC
(AMLODIPINE/VALSARTAN)

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/s/

NORMAN L STOCKBRIDGE

04/22/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 74490

Novartis Pharmaceuticals Corporation
Attention: Nancy Landzert
Associate Director
Global Regulatory CMC
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Landzert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VEA489A (amlodipine/valsartan/HCTZ) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on December 12, 2007. The purpose of the meeting was to discuss the dissolution test procedures and acceptance criteria (Q) for all three drug substances: amlodipine besylate, valsartan and HCT in your VEA489A drug product.

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

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Novartis Pharmaceuticals Corporation
Application Number:	IND 74,490
Product Name:	VEA489A fixed dose combination film-coated tablet amlodipine besylate, valsartan (Diovan®) and hydrochlorothiazide (HCT)
Meeting Requestor:	
Meeting Type:	Type C
Meeting Category:	Chemistry, Manufacturing and Controls, End of Phase 2 Follow-up Teleconference
Meeting Date and Time:	Wednesday, December 12, 2007, 0900 – 1000 ET
Meeting Location:	Teleconference
Received Briefing Package	November 9, 2007
Meeting Chair:	Ramesh Sood, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

b(4)

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of Pre-Marketing Assessment I:

Scott Goldie, PhD, Regulatory Health Project Mgr. – Quality

Ramesh Sood, PhD, Branch Chief

Prafull Shiromani, PhD, Review Chemist

Kasturi Srinivasachar, PhD, Pharmaceutical Assessment Lead

EXTERNAL ATTENDEES:

b(4)

Donna Viveio, Director, Drug Regulatory Affairs
Robert Frank Wagner, TRD Project Leader, Technical Research and Development
Roy Paul, Analytical Expert, Pharmaceutical & Analytical Development
Yatindra Joshi, Vice-President, Pharmaceutical & Analytical Development
Gangadhar Sunkara, PhD Fellow/Lead Pharmacokineticist Exploratory Clinical Development

1.0 BACKGROUND

Novartis has developed VEA489, a fixed dose combination film-coated tablet formulation containing amlodipine besylate, valsartan (Diovan®) and hydrochlorothiazide (HCT). The following five fixed-dose triple combination strengths have been developed for the market:

- 5 mg amlodipine/ 160 mg valsartan/ 12.5 mg HCT (5/160/12.5)
- 10 mg amlodipine/ 160 mg valsartan/ 12.5 mg HCT (10/160/12.5)
- 5 mg amlodipine/ 160 mg valsartan/ 25 mg HCT (5/160/25)
- 10 mg amlodipine/ 160 mg valsartan/ 25 mg HCT (10/160/25)
- 10 mg amlodipine/ 320 mg valsartan/ 25 mg HCT (10/320/25)

Novartis met with the Agency for a Type B meeting on October 13, 2004, regarding the development of a fixed-dose triple combination (VEA489) and for a pre-NDA meeting on May 9, 2007, regarding the plans for format and content of the New Drug Application (NDA). Novartis plans to submit the NDA for the fixed-dose triple combination of amlodipine besylate, valsartan and HCT for the treatment of hypertension at the end of February 2008.

On October 4, 2007, received October 5, 2007, Novartis requested a follow-up Chemistry, Manufacturing and Controls teleconference to discuss the dissolution test procedures and acceptance criteria (Q) for all three drug substances: amlodipine besylate, valsartan and HCT. The meeting was granted by the Office of New Drug Quality Assessment (ONDQA) on October 30, 2007. The corresponding briefing book provides the specific topics for discussion during the meeting (Section 2) and provides a summary of the drug substance (Section 3.1) and drug product (Section 3.2) information. The briefing book was sent on November 8, 2007, and received on November 9, 2007. The preliminary responses to the questions contained in the briefing package were archived and shared with Novartis on Monday, December 10, 2007. Novartis amended the agenda on Tuesday, December 11, 2007, providing additional preliminary feedback and discussion points, based on FDA's preliminary responses. The meeting occurred as scheduled on Wednesday, December 12, 2007. The relevant discussion points and action items are captured below.

2.0 DISCUSSION

2.1 Due to the experience gained during a drug product development, Novartis has introduced a modified dissolution method for VEA489.

2.1.1 Based on the justification and stability results, does the Agency agree with this dissolution method?

Novartis position: To assure drug product quality, Novartis has developed two dissolution test procedures for five dosage strengths of VEA489 film-coated tablets:

- for the lower dosage strengths of VEA489 film-coated tablets 5/60/12.5 mg, 10/160/12.5mg, 5/160/25 mg and 10/160/25 mg, the proposed dissolution method conditions are:
 - 900 ml,
 - pH 6.8 (phosphate buffer),
 - Apparatus 2 (paddle) at 50 RPM,
- for the highest dosage strength of VEA489 film-coated tablets 10/320/25 mg, the proposed dissolution method conditions are :
 - 900 ml,
 - pH 6.8 (phosphate buffer),
 - Apparatus 2 (paddle) at 55 RPM.

The only difference between the dissolution test procedures for the lower dosage strengths of VEA489 (5/60/12.5 mg, 10/160/12.5 mg, 5/160/25 mg and 10/160/25 mg) and the highest dosage strength (10/320/25 mg) is the paddle speed – 50 and 55 RPM, respectively. During development of the drug product, different paddle speeds were tested for all dosage strengths of VEA489 film-coated tablets. Based on these results, the increase in paddle speed from 50 to 55 RPM is proposed to minimize cone formation associated with the higher tablet weight of VEA489 10/320/25 mg. It has been confirmed that results obtained at 55 RPM for the highest dosage strength are comparable to the results obtained at 50 RPM for the lower dosage strengths of VEA489 film-coated tablets. Both paddle speeds with USP vessels provided adequate discrimination for drug product in terms of packaging and storage conditions.

Justification for selection of dissolution method parameters for VEA489 film-coated tablets and results of experimental studies during drug product development are presented in the Dissolution Method and Justification of Specification report [in the briefing book].

FDA Preliminary Response: *Agency Comment:* Provide your rationale for the selection of the dissolution method for Valsartan since you state in Section 5, that ‘the dissolution method is able to discriminate between different formulations based on different rate of dissolution of HCT and Amlodipine, but not Valsartan’.

Novartis Response to Agency Comment: In Section 5 of Novartis document Dissolution Method and Justification Report 07095, we have stated that "the dissolution method is able to discriminate between different formulations based on different rate of dissolution of HCT and Amlodipine, but not Valsartan". To further clarify, the statement was specifically referencing the three BE formulations. Figure 5-2 shows that the three BE formulations are equivalent in terms of Valsartan release at 30 minutes, but different from Valsartan 160 mg Capsule. Figure 5-1 and Figure 5-3 shows the discriminating power for Amlodipine and HCT at 30 minutes.

b(4)

Meeting Discussion: FDA acknowledged Novartis' response to FDA's preliminary responses. FDA agreed to Novartis' proposal to use 900 ml of pH 6.8 (phosphate buffer) as dissolution media in USP Apparatus 2 (paddle) at 50 RPM for the lower dosage strengths of VEA489 film-coated tablets 5/60/12.5 mg, 10/160/12.5mg, 5/160/25 mg and 10/160/25 mg. For the highest dosage strength of VEA489 film-coated tablets (10/320/25 mg) FDA agreed with the proposed dissolution method conditions of 900 mL of pH 6.8 (phosphate buffer) in Apparatus 2 (paddle) at 55 RPM. FDA/ONDQA clarified that responsibility for setting of dissolution specifications now lies within ONDQA.

Agency Recommendation: Generate dissolution data at earlier time points during the stability study of the primary stability batches, e.g. 15 or 20 minutes, in order to better evaluate your proposed Q value.

Novartis Response to Agency Recommendation: During development of VEA489 film-coated tablets, dissolution data were generated at multiple time points (e.g. 10, 15, 20, 30 and 45 minutes) for the release testing of all registration stability and pre-validation batches. Additionally, registration stability samples stored at 40°C/75 % RH, in various packages were also tested at multiple time points (15, 30, and 45 minutes)

b(4)

In summary, the current dissolution method is able to discriminate formulation changes as well as physical changes during stability for all three components (Amlodipine, HCT and Valsartan). Based on the data presented in Dissolution Method and Justification Report 07095, and dissolution data generated for the registration stability program, Novartis feel that a proposed Q = — for Amlodipine and ← for Valsartan and HCT are justified.

b(4)

Meeting Discussion: Novartis acknowledged and agreed to implement the FDA recommendation to add time points at 10, 15, 20 and 30 minutes at future stability time points and supply data to the NDA by the mid-cycle of the review. Further, the scientific justification of the dissolution method acceptance criteria will be supplied in the pharmaceutical development (PD) section of the original NDA. FDA recommended that the PD section also include a discussion of the use of different analytical methodologies used for dissolution, for example, the use of peak vessels.

2.2 Based on the registration stability data available to date, Novartis proposes the following dissolution acceptance criteria (Q) for the all three drug substances (amlodipine, valsartan, HCT).

2.2.1 Does the Agency agree with the proposed dissolution acceptance criteria?

Novartis Position: The proposed dissolution method acceptance criteria (Q) for all strengths of VEA489 film-coated tablets are as follows:

- amlodipine Q = — in 30 minutes
- valsartan Q = — in 30 minutes
- HCT Q = — in 30 minutes

b(4)

The specification has been set based on the available to date release and 6 month stability data on 15 batches within ICH storage conditions and various commercial and bulk packaging. The results and rationale for the Q acceptance criteria are presented in the Dissolution Method and Justification of Specification report [in the briefing book].

FDA Preliminary Response: We cannot comment at this time since this is a review issue and the determination will be based on your dissolution data generated at earlier time points.

Meeting Discussion: Novartis acknowledged receipt of the preliminary responses. FDA further clarified that the acceptance criteria would be based on all stages of dissolution analysis and not be restricted to stage 1. No further discussion occurred during the meeting.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

Regarding the drug product specifications: The identity test for the drug substance in the drug product specification should be specific e.g., infrared spectroscopy or a combination of tests into a single procedure, such as HPLC/UV diode array - refer to ICH Q6A.

Meeting Discussion: Novartis acknowledged receipt of the preliminary responses. No further discussion occurred during the meeting.

4.0 ACTION ITEMS

There are no other action items other than those described in the meeting discussion sections above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Linked Applications

Sponsor Name

Drug Name

IND 74490

NOVARTIS
PHARMACEUTICALS
CORP

DIOVAN(VALSARTAN/AMLODIPINE
BESYLATE

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/s/

SCOTT N GOLDIE
02/01/2008

RAMESH K SOOD
02/04/2008

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

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

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

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Transmitted via email to: kristine.tadych@novartis.com

Attention: Dr. Kristine Tadych

Sponsor: Novartis Pharmaceuticals Corporation

Phone: (862) 778-5005

Subject: Pre-NDA Meeting Minutes

Date: May 15, 2007

Pages, including this sheet: 7

From: Quynh Nguyen, Pharm.D.

Phone: 301-796-0510

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E-mail: quynh.nguyen@fda.hhs.gov

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Pre-NDA Meeting via Teleconference with Sponsor

Application Number: IND 74,490

Sponsor: Novartis Pharmaceuticals Corporation
Drug: Amlodipine/valsartan/HCTZ fixed-dose triple combination (VEA489A)

Type of Meeting: Pre-NDA
Classification: B

Meeting Date: May 9, 2007
Briefing Package Received: March 21, 2007
Confirmation Date: April 3, 2007
Meeting Request Received: March 21, 2007

Meeting Chair: Thomas Marciniak, M.D.
Recorder: Quynh Nguyen, Pharm.D.

List of Attendees:

Food and Drug Administration

Thomas Marciniak, M.D.

John Lawrence, Ph.D.
Quynh Nguyen, Pharm.D.

Deputy Director (Acting) and Medical Team Leader, Division of Cardiovascular and Renal Products (DCRP)
Statistician, Division of Biometrics I
Regulatory Health Project Manager, DCRP

Novartis Pharmaceuticals Corporation

Adrian Birch
Donna Vivelo
Kristine Tadych, Pharm.D.
Robert Glazer, M.D.
Joseph Yen
Tom Chiang
Gangahar Sunkara, Ph.D.
Pritam Sahota, Ph.D.
Georgia Tarnesby, M.D.
Angelo Trapani, Ph.D.
Valentin Curt, M.D.

Vice President, Drug Regulatory Affairs
Director, Drug Regulatory Affairs
Associate Director, Drug Regulatory Affairs
Executive Director, Clinical Development & Medical Affairs
Associate Director, Biostatistics
Director, Biostatistics
Associate Director, Exploratory Development
Director, Preclinical Safety
Executive Director, Drug Regulatory Affairs
Clinical Trial Manager, Clinical Development & Medical Affairs
Director, Clinical Development & Medical Affairs

b(4)

BACKGROUND

Novartis plans to submit an NDA for amlodipine/valsartan/HCTZ fixed-dose triple combination product in February 2008. The proposed indication is for the treatment of hypertension. This Pre-NDA meeting via teleconference was scheduled to discuss the content and format of the proposed NDA. The Division's Preliminary Responses were sent to the sponsor on May 7, 2007. The sponsor agreed with the Division's Preliminary Responses, except for Clinical/Statistical Question 3. This question was discussed in further detail during the meeting as noted below.

DISCUSSION

Regulatory

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

Preliminary Response

Yes.

Clinical/Statistical

1. Is the Division in agreement with our proposal for the Summary of Clinical Efficacy outlined in Section 3.2

Preliminary Response

Yes.

2. Is the Division in agreement with our proposal not to pool safety data for the Summary of Clinical Safety (SCS) outlined in Section 3.3?

Preliminary Response

Yes.

3. Is the Division in agreement with our proposal to present efficacy and safety data summarized by randomized treatment regimen (per study designs/objectives) without additional data cuts for subgroups of patients with optional, open-label exposure to the triple combination in those studies listed in Section 3.1.2?

Preliminary Response

No. Please submit the efficacy and safety data summarized by randomized treatment regimen (per study designs/objectives) with the additional data cuts for safety analyses for subgroups of patients with open-label exposure to the triple combination in those studies listed in Section 3.1.2.

Discussion during Meeting

The sponsor stated that the objective of the eight studies listed in Section 3.1.2 was to evaluate the dual combinations. In seven of these studies, the triple combination exposure was due to the optional, open-label addition of either hydrochlorothiazide or amlodipine to the dual combinations during the late phase of the study. The one remaining study is an ongoing extension study in which patients are given triple combination after not responding to dual therapy in the primary core study. The sponsor provided a rationale on why they propose to present efficacy and safety data summarized by randomized treatment regimen without additional data cuts for subgroups of patients with the optional, open-label exposure to the triple combination. Dr. Marciniak replied that the sponsor's rationale applied to the limitations of all open-label extension studies. The sponsor pointed out that the studies listed in Section 3.1.2 were intended to be short-term supportive studies and would contribute only limited safety information. The pivotal study to assess the efficacy and safety of the triple combination would be study VEA 2302. Per a Special Protocol Assessment (SPA) agreement with the Agency (SPA submitted to IND 65,174), the Agency had agreed with the sponsor's approach not to conduct an open-label safety extension for this triple combination and that short-term safety data could be obtained from study VEA 2302 and other safety data from post-marketing information.

After further discussion, the sponsor proposed that for each of the short-term studies listed in section 3.1.2, which will be complete at the time of the submission (VAA A2401, VAA A2402, VAA A2403, VAH BUS04, and VAH BDE13), they would provide an additional data cut: overall summary of adverse events by body system and in alphabetical order. These additional data cuts would be in patients with exposure to the triple combination and would include adverse events that occurred while these patients were receiving the triple combination. For the long-term extension study, VAA 2201E1, the summary of adverse events for the subgroup of patients ever exposed to the triple combination had already been provided in the original NDA submission for the dual combination of amlodipine/valsartan (NDA 21-990/Exforge), and the sponsor planned to include this summary in the VEA NDA. The Division agreed with the sponsor's proposal.

4. Is the Division in agreement with our proposal not to submit data from the two trials (i.e., studies VAH B1303E and VAA A1302) conducted in Japan because these studies did not mandate the use of amlodipine or HCTZ but rather any drugs in their respective class?

Preliminary Response

Yes.

5. Is the Division in agreement with our proposal for the CRT submissions outlined in Section 3.4.1?

Preliminary Response

No. Please submit the CRTs (SAS data sets of the raw and derived data) for the VAA and VAH studies that are completed at the time of submission.

Discussion during Meeting

The sponsor agreed to submit CRTs (SAS data sets of the raw and derived data) for the VAA and VAH studies that are completed at the time of submission. The sponsor will contact the Division regarding additional statistical questions at a later time.

6. We anticipate an NDA submission for this combination to be submitted February 2008. Is the Division in agreement with the cut-off date of October 31, 2007 for clinical study reports and data cut-off date of November 30, 2007 for ongoing studies?

Preliminary Response

Yes.

Technical

1. Novartis proposes to include the one executed batch record, only. It will be representative for all five strengths due to the fact that the manufacturing process is the same and it contains all the excipients which are common to the other 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

Yes.

2. Novartis proposes to include the certificates of analysis of the non-compendial excipients in the regional section (3.2.R.1) – Methods Validation Package (R.3.P), only. Certificates of analysis of the excipients released according to USP/NF will not be included in the regional section. Does the Division agree with this approach?

Preliminary Response

No. Representative COAs for both non-compendial and compendial excipients should be provided, preferably in Section 3.2.P.4. If this information is submitted elsewhere (e.g., Section 3.2.R.1), then Section 3.2.P.4 should contain a statement clearly identifying the location.

3. Novartis will use the proposal of providing 6 month drug product stability data at the time of NDA submission and will follow the attached registration stability protocol [RSP6170-2A], unless otherwise directed by the Agency. Twelve-month drug product stability data will be provided to the Agency within 6 months after the submission date. Does the Division agree with this approach?

Preliminary Response

Yes, provided the additional stability data are available within 5 months after the initial NDA submission. A rationale for not performing the Microbial Limits Test at any time point in the stability program for physician samples should be provided.

Additional Comments

CMC

- In the drug product specification, the Identity Test by HPLC retention time alone is not considered sufficient (ICH Q6A). A more specific test should be proposed.
- We expect moisture content to be included in the stability testing of the drug product unless adequate justification can be provided for its omission.
- A complete list of all manufacturing, testing and packaging facilities for both drug substance and drug product should be submitted as an attachment to Form 356h.
- DMF letters of authorization for amlodipine drug substance should be provided in the NDA, even if they were submitted to IND 74,490.

Other

- If you believe that there are product risks that merit more than conventional professional product labeling (i.e., package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then we encourage you to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:
 - Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fml.htm>
 - Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fml.htm>
 - Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>
- If there is any information on product medication errors from the premarketing clinical experience, we request that this information be submitted with the NDA application.

- We encourage you to submit the proprietary name and all associated labels and labeling for review as soon as available.

CONCLUSION

This meeting was scheduled to reach agreement on the content and format of the proposed NDA for amlodipine/valsartan/HCTZ fixed-dose triple combination product. The sponsor plans to submit the NDA in February 2008.

If you have any questions, please call:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Thomas Marciniak, M.D.
Deputy Director (Acting) and Medical Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Rd:
T Marciniak 5/14/07
J Lawrence 5/9/07

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/s/

Thomas Marciniak
5/15/2007 11:46:09 AM

This is a memo to file: on 22 May 2006, the following email was sent to the sponsor:

Dear Donna,

The following response is provided by the statistical reviewer regarding IND 74,490. Please let me now if you have any questions or concerns.

Best regards, Cheryl Ann

Statistical Issues

1. Hochberg's procedure controls the error rate only under certain strict conditions that are difficult to verify. Although systolic and diastolic blood pressure may be positively correlated, that does not ensure that the maximum of the 3 p-values for diastolic BP will be positively correlated with the maximum for systolic BP. Moreover, simply being positively correlated is not a sufficient condition for Hochberg's procedure to be valid. Therefore, we still recommend Holm's procedure because it is valid without any restrictions on the joint distribution of the test statistics and is less conservative than the original proposed procedure in the protocol.

LCDR Cheryl Ann Borden, MSN, R.N., CCRN, CCNS
Regulatory Health Project Manager
Office of Drug Evaluation 1
Division of Cardio-Renal Drug Products
WO22 RM 4165, HFD-110
Silver Spring, MD 20993
301.796.1046
bordenc@cdcr.fda.gov

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/s/

Cheryl Borden
5/22/2006 11:52:02 AM
CSO

Telecon Minutes

Date: 9 January 2006
Sponsor: Novartis Pharmaceuticals
Subject: Valsartan 320/HCTZ 25/amlodipine 10
Type of Meeting: Telecon

FDA Participants:

Shari Targum, M.D., HFD-110; Medical Officer
LCDR Nhi Beasley, Pharm.D., HFD-860, Clinical Pharmacology Reviewer
LCDR Cheryl Ann Borden, MSN, RN, HFD-110, Project Manager

Sponsor Participants:

Donna Viveló, Regulatory Affairs
Robert Glazer, M.D., Clinical Research
Gangadhar Sunkara, Ph.D., Clinical Pharmacology

BACKGROUND:

The Division requested a telecon to discuss the sponsor's proposed drug interaction study (serial #49) which will use a lower dose than the dosage submitted in a previous SPA.

DISCUSSION POINTS:

Biopharmaceutics:

The telecon was opened with brief introductions. Dr. Targum queried the sponsor regarding the proposed dosage to be studied in the PK drug-drug interaction study submitted in 65,174/S-049.

Novartis responded that the study consisted of healthy volunteers and they felt it was unsafe to use the higher dose as proposed in the SPA submitted in October.

Drs. Targum and Beasley stated that since the sponsor is studying valsartan 320 /HCTZ 25 /amlodipine 10 mg in the SPA, characterization of the pharmacokinetic drug interaction at the highest dose is needed in the drug interaction study. The sponsor proposed to study half the dose of each drug however, the lack of a signal in such a study would not preclude a signal with the higher doses. The sponsor expressed a safety concern over using the high dose in healthy volunteers. Drs. Targum and Beasley offered three suggestions:

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/s/

Shari Targum
1/12/2006 02:15:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,174

Novartis Pharmaceuticals Corporation
Attention: Ms. Donna M. Vivelo
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Diovan HCT plus amlodipine (valsartan/hydrochlorothiazide plus amlodipine) Tablets.

We also refer to your 15 September 2005, serial number 045, request for a special clinical protocol assessment, received 22 September 2005. The protocol is entitled Protocol VEA 2303.

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

Questions:

1. Does the Division agree with the VEA 2302 study design to support registration of the fixed combination of DiovanHCT plus amlodipine for patients whose blood pressure has not been adequately controlled by any of the dual therapy with these classes of drugs?

Division response: We agree with the basic structure of your proposed study. However, we have several comments and reservations, as listed in the answers to Questions 3-6, below.

2. Does the Division agree with the inclusion and exclusion criteria for the study?

Division response: The inclusion and exclusion criteria are acceptable.

3. Does the Division agree with the diastolic and systolic blood pressure criteria for randomization?

Division response: We agree with the blood pressure criteria for randomization; however, the specific process to be used to determine qualifying blood pressures should be delineated in the protocol (e.g., will the qualifying blood pressure be determined as the mean of three blood pressure measurements, or some other method?).

4. Does the Division agree with the choice of the primary efficacy variable and the statistical analysis plan?

Division response:

- Although we agree with your proposed primary study endpoints (mean sitting diastolic blood pressure [MSDBP] and mean sitting systolic blood pressure [MSSBP]), we do not believe that

your planned secondary endpoints would provide clinically meaningful data (blood pressure control rates; systolic and/or diastolic). In the event that the triple combination is approved, it is unlikely that response rate or control rate information will be appropriate for labeling.

- Because the study does not include a placebo group, the absolute blood pressure lowering effects of the combination product will not be evaluated. If you decide not to add a placebo arm to the study, then we recommend the utilization of 24-hour ambulatory blood pressure monitoring, in order to decrease the impact of placebo effects.
 - Your sample size calculation is based on the assumption of a true treatment difference of 2 mmHg in MSDBP and 3.5 mm Hg in MSSBP between the triple and dual therapies. If this trial shows a statistically significant but small effect size, then the Division may not accept the study as showing a clinically meaningful effect. If you resubmit this protocol, please provide a rationale for what you consider to be a clinically meaningful treatment effect in lowering systolic and diastolic blood pressure. Here too, ABPM data would perhaps enable you to support the benefits of a small 24-hour mean effect.
 - Your proposed method of dividing the overall type I error rate of 0.05 by two to control the error rate for the two endpoints (systolic and diastolic BP) is acceptable. However, there are other less conservative ways of controlling the overall error rate. We recommend using Holm's procedure.
 - Please clarify whether "region" (used as a stratification factor for randomization procedure) is synonymous with "center" (used as an explanatory variable in the analysis of covariance). You may need to develop an algorithm that is used for combining small centers (regions).
5. Consistent with Agency feedback we received regarding Lotrel/HXTZ (IND 35,965) we will not conduct an open-label safety extension to VEA for this triple combination. Short-term safety data will be obtained from VEA 2302 and other safety data can be obtained from post-marketing information. Does the Division agree with this approach?

Division response: We agree with this approach.

6. Does the Division agree with the triple combination doses selected for development and marketing?

Division response: There is no objection to using valsartan 320 mg once daily in the study. However, because there is little evidence to suggest that the blood pressure lowering effects of the 320 mg and 160 mg doses, administered daily, are distinguishable, it may be difficult to justify (in labeling) a combination product that includes valsartan 320 mg once daily.

In addition, we have the following comments:

- Subjects who discontinue the study drug are to be withdrawn from the investigation. We suggest that you continue to monitor these subjects until the end of the study, if possible.
- We suggest an additional blood draw for chemistries (including potassium, BUN, and creatinine) at Week 3.
- There are several references in the protocol to Section 7.4 (for example, on page 25). However, we were unable to locate Section 7.4.
- For the individual patients, blood pressures should be recorded in the same arm throughout the study.
- Because response to therapy may be affected by race, you might consider stratification of randomization by race.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600

IND 65,174
Page 3

Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at <http://www.fda.gov/cder/guidance/index.htm>. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS
Regulatory Health Project Manager
at 301-796-1046.

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
11/3/2005 06:58:43 AM

Diovan®HCT in combo with amlodipine

Meeting Minutes

Type B Meeting between Novartis Pharmaceutical Corporation and the FDA

Date: October 13, 2004
Sponsor: Novartis Pharmaceutical Corporation
Subject: Diovan® HCT (valsartan/HCTZ) plus amlodipine besylate
Triple Combination Tablets
IND 65,174
Type of Meeting: Type B

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation
Norman Stockbridge, M.D., Ph.D., HFD-110, Acting Director, Division of Cardio-Renal Drug Products
Thomas Marciniak M.D., HFD-110, Acting Deputy Division Director
Abraham Karkowsky M.D., Ph.D, HFD-110, Medical Team Leader
Patrick Marroum, Ph.D., HFD-860, Team Leader, Clinical Pharmacology/ Biopharmaceutics
Albert F. DeFelice, Ph.D., HFD-110, Pharmacology Team Leader
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
James Hung, Ph.D., HFD-710, Statistics Team Leader
Edward J. Fromm, R.Ph., HFD-110, Chief, Project Management Staff
LCDR Cheryl Ann Borden, MSN, R.N., HFD-110, Regulatory Health Project Manager

FDA Participants via Telecon:

David G. Orloff, M.D., HFD-510, Division Director, Division of Metabolic & Endocrine Drug Products
Mary H. Parks, M.D., HFD-510, Deputy Director, Division of Metabolic & Endocrine Drug Products

Sponsor Participants:

Adrian Birch, Executive Director, Drug Regulatory Affairs
Donna Vivelo, Director, Drug Regulatory Affairs
William Daley, MD, Executive Director, Cardiovascular Clinical Development & Medical Affairs
Yann Tong Chiang, PhD, Director, Biostatistics
Joanna Cheng, PhD, Senior Associate Director, Biostatistics
Madhu Pudipeddi, PhD, Assoc. Director, Pharmaceutical Development, Technical Res. & Dev.
Gangadhar Sunkara, PhD, Fellow/Lead Pharmacokineticist, Exploratory Clinical Development
Pratapa Prasad, PhD., Director, Early Clinical Development
Pritam Sahota, PhD, Director of Pathology, Preclinical Safety
Chin Koerner, Director, Regulatory Liaison Office

BACKGROUND: Sponsor is seeking guidance on the preclinical, clinical, biopharmaceutical development program to support the marketing authorization for the triple combination product of Diovan®HCT (valsartan and hydrochlorothiazide) in combination with amlodipine besylate for the treatment of hypertension.

DISCUSSION POINTS:

The meeting was opened by Donna Vivelo of Novartis with a brief overview utilizing the following slide presentation that outlined the proposed use of the combination and the study they planned to do.

Diovan®HCT and Amlodipine Fixed Combination Tablets

- Triple fixed-combination product containing Diovan®HCT (valsartan/HCTZ) and amlodipine besylate for the treatment of patients with hypertension
- Titration pathways include:
 - Patients who are uncontrolled on Diovan®HCT
 - Patients who are uncontrolled on valsartan/amlodipine
 - Replacement therapy for patients taking separate components

3

Diovan®HCT and Amlodipine Fixed Combination Tablets

- Doses to be studied clinically range from 80/12.5/5mg to 320/25/10mg to adequately evaluate dose response
- Doses to be commercialized will be chosen based on data from the multifactorial trial A2302

Val/ HCTZ Val/aml	80/12.5	160/12.5	160/25	320/12.5	320/25
80/5	80/12.5/5				
160/5		160/12.5/5			
160/10		160/12.5/10	160/25/10		
320/5				320/12.5/5	
320/10				320/12.5/10	320/25/10

4

Review of Questions submitted to the Agency by Novartis:

1. Does the Division agree with the planned preclinical safety development program outlined in Section 3.7?

Agency response: It is acceptable.

Diovan®HCT in combo with amlodipine

2. The clinical development plan to support the global registration of the triple fixed combination is outlined in Section 4. (includes PK and the factorial study shown in the second slide).

Background: Novartis is approaching the development of this triple fixed combination from a global perspective in order to meet international health authority requirements.

The proposed clinical program for the Diovan®HCT plus amlodipine fixed dose combination product consists of one multifactorial study, 58 week open label extension trial, and two trials in patients who fail to respond to each of the dual therapy components of the triple combination; non-responders to Diovan®HCT and non-responders to valsartan/amlodipine.

- a. Does the Division have any comments on the clinical development plan?

Agency response: The clinical development plan is acceptable. Specifically, the proposed study is acceptable.

- b. Does the Division agree with the statistical analysis plan outlined for the combined multifactorial study A2302 in Section 4.4.1 and Attachment 1?

Background: Three valsartan/HCTZ/amlodipine triple combination doses are specified as primary for the statistical assessment. They are 160/25/10mg, 320/12.5/10mg and 320/25/10 mg. Statistical evidence for the primary objective is considered to be achieved if there exists at least one primary triple combination dose statistically more effective than both of its dual therapy component doses.

Agency response: We propose a different design. (See response to 2c below).

- c. If the primary objective is achieved in A2302 by showing that at least one of the three selected triple combination doses (i.e., 320/25/10mg, 320/12.5/10mg or 160/25/10mg) is statistically more effective than both of its dual therapy component doses, and the other triple combination doses do not display negative trends when compared to their dual component doses, are all triple combination doses included in the study approvable? (Refer to Attachment 1).

Agency response: Dr. Temple proposed a simplification to the sponsor's proposed plan: that only the high doses of the component are studied. The triple (320/10/25) should be shown to be statistically superior to the high dose of double combinations (320/25), (320/10), and (10/25), thereby showing a contribution of each component. This would be a 4 arm study. These data would also support the combinations using lower doses, e.g., if 10 mg of amlodipine is shown to have an additive effect, then we would consider 5 mg to be additive as well.

Novartis asked if they missed on one cell would they still get labeling on the other two cells?

Agency response: Dr. Temple responded they would not; they would need to show that the triple combination is superior to all 3 double combinations, which would show that each component contributed to the antihypertensive effect. He noted that our proposal would produce a much smaller study, albeit one with more risk.

Novartis asked if their current proposal was completely unacceptable and noted that the new study design was contrary to previous advice given for the Lotrel program.

Agency response: Dr. Temple said the sponsor could do the planned larger study with multiple dosing groups, but that each drug group would have to show a statistically significant contribution to the blood pressure effect. That would not mean that each cell would need to show an effect, but each drug would need to. Dr. Stockbridge noted that

Diovan®HCT in combo with amlodipine

the design proposed does not compare the triple combinations with double combinations lacking valsartan, so they may not isolate the effect of valsartan; although there is an opportunity to see a valsartan dose-response the deliveries will be smaller than a comparison of valsartan and a zero dose of valsartan. Dr. Temple said it is important to include maximal doses of each component so that the component will have a reasonable chance to an additive effect.

Novartis asked if they could submit a Special Protocol Assessment regarding the dose groups they want for the study.

Agency response: Dr. Temple said it was acceptable. Dr. Stockbridge noted that the sponsor should attempt to reduce the number of dose groups that are not helpful. For example, the 80/12.5/5 mg combination should not be encouraged for initial therapy, since a tenet of combination therapy is that each component should be maximized before adding another drug. This holds true especially for valsartan as it has few bothersome side effects.

- d. From previous interactions with the Division, we presume that data from the longterm safety study (section 4.4.2) and the non-responder studies (section 4.4.3) are not required for NDA submission. Would the Division agree with our approach to file an NDA when results of the multifactorial study (A2302, section 4.4.1) are available?

Agency response: It is difficult to comment without reviewing the data.

- e. Or pivotal study A2302 will not employ a placebo arm because of ethical concerns in a population that includes severe hypertensives. We would like to have a discussion regarding how our clinical study results would be discussed in labeling. For example, we assume we would make a reference to incremental BP reductions for a triple combination compared to one or more corresponding double combinations employing two of the same doses contained in the triple. From our perspective this type of information would be needed by physicians to guide clinical treatment.

Agency response: There is a possibility of a table showing the effect of incremental titration on blood pressure.

3. The biopharmaceutics development plan to support registration of the fixed triple combination product is outlined in Section 5. Does the Division agree with the planned definitive bioequivalence studies and planned biowaiver strategy?

Agency response: The planned definitive BE studies are adequate. The biowaiver strategy is dependent on the doses you will be testing.

4. The envisioned labeling for this fixed triple combination product will allow titration from either dual combination, i.e., from Diovan® HCT → Diovan HCT plus amlodipine, or Diovan/Amlodipine → Diovan® HCT plus amlodipine. The biopharmaceutics development plan will test the bioequivalence of the new fixed triple combination dosage form with the market formulations of Diovan®HCT and Norvasc®. (Separately, Novartis will have demonstrated the bioequivalence of the Diovan/amlodipine formulation with each of its component market formulations as a basis of that product's approval.) Is the biopharmaceutical development plan sufficient as planned to support both titration schemes proposed above?

Agency response: Dr. Temple replied that there would be no initial therapy claim for this triple combination product, as valsartan/HCTZ has been shown to be well tolerated, but amlodipine has some serious side effects that would not make it suitable for initial therapy.

Diovan®HCT in combo with amlodipine

Novartis responded that the doses they market would have to be considered, as there are 25 possible doses based on the monotherapy. Currently there are only certain doubles on the market and the reason behind going to the triple is to reduce some of these combinations as well as for convenience for the patient.

Other:

DiovanHCT/amlodipine: If we were able to identify an appropriate patient subgroup which meet the futility and urgency criteria, is it possible to obtain a restricted first line indication for that subset of patients?

Agency response: We will consider that after submission of the data.

SUMMARY/ RECOMMENDATIONS:

Novartis will send in a formal proposal on what dose groups they plan to study.

Signature recorder : (see appended electronic signature page)
LCDR Cheryl Ann Borden, MSN, R.N.

Concurrence, Chair: (see appended electronic signature page)
Robert Temple, M.D.

Fromm 10/20/04, 11/10/04
Hung 10/26/04, 11/10/04
Srinivasachar 10-26-04
DeFelice 10/27/04
Marroum 10/27/04
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/s/

Robert Temple
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