CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-985

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

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

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

NDA NUMBER
21-985

NAME OF APPLICANT / NDA HOLDER
Novartis Pharmaceuticals Corporation

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

TRADE NAME (OR PROPOSED TRADE NAME)
RASILEZ (proposed)

ACTIVE INGREDIENT(S)	STRENGTH(S)
Aliskiren	150 mg and 300 mg

DOSAGE FORM
Tablets

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

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

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

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

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
5,559,111	09/24/1996	04/04/2015

d. Name of Patent Owner	Address *(of Patent Owner)*	
Novartis Corporation	One Health Plaza	
	City/State East Hanover, NJ	
	ZIP Code 07936	FAX Number *(if available)*
	Telephone Number (888) 669-6682	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☑ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

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

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☑ Yes	☐ No
4.2 Claim Number (*as listed in the patent*) 9	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

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

6. Declaration Certification

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
Gregory Ferraro	10/25/2005

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

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☑ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Gregory Ferraro	
Address One Health Plaza, Bldg 104	City/State East Hanover, NJ
ZIP Code 07936	Telephone Number (862) 778-7831
FAX Number *(if available)* (973) 781-8064	E-Mail Address *(if available)* gregory.ferraro@novartis.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html.*

First Section

Complete all items in this section.

1. General Section

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

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

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

2. Drug Substance (Active Ingredient)

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

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

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

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

4. Method of Use

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

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

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

EXCLUSIVITY SUMMARY

NDA # 21-985 SUPPL # HFD # 110

Trade Name Tekturna

Generic Name aliskiren

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known 3/5/07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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

YES ☒ NO ☐

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

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#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES ☐ NO ☐

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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"):

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

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

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

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

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

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

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

YES ☐ NO ☐

If yes, explain:

Name of person completing form: John David
Title: RHPM
Date: 3/5/07

Name of Office/Division Director signing form: Robert Temple, M.D.
Title: Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/

Robert Temple
3/5/2007 05:06:34 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-985 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: 2/13/06 **PDUFA Goal Date:** 3/13/07

HFD 110 **Trade and generic names/dosage form:** Tekturna (aliskiren) 150 mg and 300 mg tablets

Applicant: Novartis Pharmaceuticals Corporation **Therapeutic Class:** renin inhibitor

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

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

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** _____

Each indication covered by current application under review must have pediatric studies: ***Deferred***

Number of indications for this application(s): 1

Indication #1: hypertension

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- x **No: Please check all that apply:** X **Partial Waiver** X **Deferred** ____ **Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

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

/s/

John David
3/6/2007 03:22:04 PM

NDA 21-985

Rasilez® (aliskiren) Tablets

New Drug Application- 120 Day Safety Update

Debarment 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.

Kimberly O Dickerson

Kimberly Dickerson, Pharm. D
Associate Director
Drug Regulatory Affairs

06/12/06
Date

NDA 21-985

Rasilez® (aliskiren) Tablets

New Drug Application

Debarment 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.

Kimberly D Dickerson

Kimberly Dickerson, Pharm. D
Assistant Director
Drug Regulatory Affairs

01/16/06
Date

ACTION PACKAGE CHECKLIST

Application Information			
BLA # N/A NDA # 21-985	BLA STN# N/A NDA Supplement # N/A	If NDA, Efficacy Supplement Type N/A	
Proprietary Name: Tekturna Established Name: aliskiren Dosage Form: 150 mg and 300 mg tablets		Applicant: Novartis Pharmaceuticals Corporation	
RPM: John David		Division: Cardiovascular and Renal Products	Phone # 301-796-1059

NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 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)): Provide a brief explanation of how this product is different from the listed drug. ☐ 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.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	March 13, 2007 March 5, 2007
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): New Molecular Entity (NME)

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

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

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

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☒ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☒ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

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

within the 45-day period). *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*).* *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.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	OD 3/5/07, DD 2/28/07
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	3/5/07
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	3/5/07
• Original applicant-proposed labeling	2/10/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	3/5/07
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	3/5/07
• Original applicant-proposed labeling	2/10/06
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	1/16/07
• Most recent applicant-proposed labeling	1/26/07
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 2/27/07, 11/30/06, 10/27/06, 8/17/06 ☐ DSRCS ☒ DDMAC 3/2/06 ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	PM overview 3/6//07 Filing review 10/16/06
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	 N/A N/A
❖ Pediatric Page (all actions)	☒ 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. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	Approval Letter
• Incoming submission documenting commitment	Submission dated 3/5/07, 2/27/07
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	1/16/07, 12/12/06, 12/11/06, 12/8/06 (2), 11/22/06, 8/23/06 (2), 8/16/06, 7/25/07, 4/24/06, 11/23/05, 9/7/05, 6/27/05, 6/20/05, 4/26/05, 4/19/05, 9/29/04, 9/28/04, 8/26/04, 7/28/04, 6/3/04, 5/27/04, 4/28/04, 3/4/04, 5/29/03, 10/30/02, 9/5/02, 8/29/01, 7/31/01
❖ Internal memoranda, telecons, email, etc.	Pre-Approval Safety 11/16/06
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	11/16/06
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 4/20/05
• EOP2 meeting *(indicate date)*	☐ No mtg 2/11/04
• Other (e.g., EOP2a, CMC pilot programs)	9/22/04
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	N/A
• 48-hour alert or minutes, if available	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	11/20/06, 12/21/06, 2/14/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☐ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☒ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☒ Review & FONSI *(indicate date of review)*	8/4/06
• ☒ Review & Environmental Impact Statement *(indicate date of each review)*	5/11/06
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	

❖ NDAs: Facilities inspections (include EER printout)	Date completed: 3/8/06 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	N/A ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/28/06, 2/13/07, 2/20/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 9/5/06
❖ ECAC/CAC report/memo of meeting	9/7/06
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	2/26/07, 12/7/06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	5/10/06
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None 11/7/06 2/1/07
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	Refer to clinical review
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	Refer to clinical review
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	8/14/06, 8/16/06
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☒ None Clinical/Statistical Combined
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2/28/07, 1/11/07

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/

John David
3/6/2007 03:10:28 PM

RHPM Overview of NDA 21-985
Tekturna (aliskiren) 150 mg and 300 mg tablets
March 6, 2007

Sponsor:	Novartis Pharmaceuticals Corporation
Type:	1S
Receipt Date:	February 13, 2006
User Fee Goal Date:	March 13, 2007
AP Letter Issued:	March 5, 2007
Final Draft Labeling:	March 5, 2007 (Enclosed in the AP letter)

Background
Novartis Pharmaceuticals Corporation submitted this NDA for Tekturna (aliskiren) Tablets for the treatment of hypertension, alone and in combination with other antihypertensive agents. They indicate that aliskiren is the first renin inhibitor to demonstrate efficacy and safety in a hypertensive population and consider aliskiren to be a significant new product for the treatment of hypertension. Results of the development program are included in this application and support the registration of aliskiren for the treatment of hypertension, alone and in combination with other antihypertensive agents. The purpose of this submission is to gain marketing approval for the 150mg and 300mg dosage strengths of aliskiren.

Office Director's Memorandum
See Dr. Temple's memo dated March 5, 2007

Division Director's Memorandum
In his Division Director's memo dated 2/28/07, Dr. Stockbridge noted in his Division Director's Memo dated February 28, 2007 support for the approval of aliskiren for the treatment of hypertension.

Medical Review
In his review dated February 26, 2007, Dr. Marciniak states that he recommends approval of aliskiren for the treatment of hypertension in adults. The one issue outstanding from his review of the original NDA submission was whether there was substantial evidence conforming that aliskiren does not cause colonic mucosal hyperplasia in humans as it does in rodents. He reviewed the results of a colonoscopy biopsy study in humans that was negative, i.e., there was no evidence of colonic mucosal hyperplasia after exposure to aliskiren 300 mg daily, the maximum recommended human dosage, for eight weeks. In rodents hyperplasia was detected after exposure for a few weeks. This human colonic biopsy study is reassuring that aliskiren does not cause hyperplasia in humans. He also reviewed the results of a second aliskiren/valsartan combination study. This study shows that the combination of aliskiren and valsartan, each at the maximum recommended dosage, provides incremental reductions in blood pressure over that produced by the corresponding monotherapies. These results are relevant to the labeling of aliskiren monotherapy for use alone or in combination with other antihypertensives because an initial study of the combination failed to show an incremental benefit. This study included reasonable numbers of blacks and demonstrated blood pressure reductions with the monotherapy in blacks. All of the findings from this study will be incorporated into the labeling and will help clinicians in understanding how to use this drug.

Labeling recommendations were attached to the medical review dated December 7, 2006.

In regards to additional mandatory phase 4 studies for this NDA. The sponsor is planning large outcome trials in heart failure and in high risk coronary artery disease patients. Dr. Marciniak recommends that the sponsor incorporate specific questions regarding the occurrences of colonoscopies, colonic polyps, intestinal cancers, or other intestinal pathology in these patients. The sponsor should collect colonoscopy reports and reports of intestinal surgery in these patients. Please see the agreed upon phase 4 commitments:

1. Deferred pediatric study under PREA for the treatment of hypertension in pediatric patients ages 6 to 16 years.
   Final Report Submission: March 5, 2009

We remind you of your other postmarketing study commitments in your submission dated February 27 and March 5, 2007. These commitments are listed below.

2. To establish an assay method and acceptance criterion for — ,PP100 —. Assay method and assay specification will be introduced into the testing monograph No. RM_5000702 for ⌣ post approval by March 2007. The revised testing monograph will be submitted to FDA in the first NDA Annual Report.
3. To re-evaluate the specifications for the water content when further data are available from the additional manufacturing sites. You expect to have this data evaluation completed by June 2007.
   Final Report Submission: by 08/07
4. To submit the results of the cellular markers of proliferation and apoptosis from Study 2103 as soon as they are available, but no later than September 2007.
   Final Report Submission: by 09/07
5. To include intestinal procedures and neoplasms and angioedema as events of special interest in your proposed ALTITUDE trial as detailed in their special protocol assessment letters. You committed to providing safety information and periodic summaries during the ALTITUDE trial for the parameters of special interest. The data should be submitted when the final study report comes in. The periodic summaries will include:
   - Monthly line listings of suspected/non suspected SAE and non serious AE (reported in the previous month)
   - Aggregate summaries (cumulative) of suspected/non suspected SAE and non-serious AE in PSUR semi-annually for the first 2 years post-launch and annually thereafter.

   Protocol Submission (including case report forms): by 09/07
   Study Completion Date: by 09/11
   Final Report Submission: by 03/12
6. To incorporate a colonoscopy substudy into your proposed long-term outcome study. The colonoscopy substudy should include colonoscopies performed at baseline and after drug treatment for 12 months or longer. This study should be powered to rule out a doubling in the rate of cancerous or precancerous lesions. You should discuss this substudy with the Agency.
   Protocol Submission: by 09/07
   Study Completion Date: by 02/09
   Final Report Submission: by 05/09
7. You should provide evidence that it is not likely to be clinically useful to give aliskiren in a twice-daily dosing regimen to patients whose blood pressure is not controlled on the highest recommended dose given once daily. These data could come from a study comparing once- and twice-daily dosing, but the Division would consider alternative strategies to address this issue.
   Protocol Agreement: by 06/07
   Final Report Submission: by 02/09

Refer to the financial disclosure is as noted on page 32 of the medical review dated December 7, 2006. Refer also to page 5 of the medical review addendum dated February 26, 2007 for additional financial disclosure information.

Pharmacology Review
In his review, Dr. Jagadeesh states that this NDA is recommended for approval and the revised labeling is acceptable, from the perspective of pharmacology/toxicology. No significant drug-specific adverse effects were noted.

Biopharmaceutical Review
Refer to Dr. Velazquez of the Office of Clinical Pharmacology and Biopharmaceutics review dated January 1, 2007.

Refer to the above listed Phase IV Commitments.

Labeling recommendations are noted in the biopharmaceutical review.

Chemistry Review
In his review, Dr. Ysern states that adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf live. Based on the evaluation of the provided CMC information, from the chemistry viewpoint this NDA can be approved. Based on the stability data submitted, an expiry of 24 months is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Protect from moisture.

Refer to the above listed Phase IV Commitments.

The sponsor's claim for categorical exclusion from the Environmental Assessment is satisfactory.

Statistical Review
There was no statistical review completed for this NDA. The medical reviewer consulted with the assigned statistician for this NDA.

DSI
In his memorandum, Dr. Chu of Division of Scientific Investigations recommended the following in his review dated August 16, 2006:

In general the sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigation. The inspection of documents support that audited subjects existed, signed informed consent prior to enrolling in the studies, and received assigned medications. The finding at Dr. Lipetz's site in regard to Protocol No: SPP100A 2308 documents a violation of not following the investigational plan. The findings at Dr. Chandler's site in regard to protocol No: SPP100A 2201 document violations regarding not following the investigational plan, not maintaining adequate and accurate case histories that record all observations and other data pertinent to the investigation, and not reporting an unanticipated problem involving risks to human subjects to the IRB. The majority of the data at these sites appear acceptable in support of this NDA. However, due to problems noted above at Dr. Chandler's site in regards to Protocol No: SPP100A 2201, for not adequately and accurate recording the data for the primary efficacy endpoint from the source document into the electronic case report forms, DSI recommends that the review division evaluate whether these discrepancies impact the overall data from this site in support of this NDA.

Pediatric Rule
Aliskiren was granted a deferral of the pediatric study under PREA for the treatment of hypertension in pediatric patients ages 6 to 17 years in the original New Drug Application for aliskiren (refer to IND 62, 976 letter dated August 26, 2004) and the final report submission is due 2 years after approval for use in adults.

We reference the deferral granted on August 26, 2004, for the pediatric study requirement for this application. We reviewed the sponsor's submission and agreed that a partial waiver is justified for pediatric studies in patients 0-6 years due to too few patients < 6 years to study. We deferred submission of there pediatric studies for ages 6 to 16 years until March 5, 2009.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

Deferred pediatric study under PREA for the treatment of hypertension in pediatric patients ages 6 to 16 years.
Final Report Submission: March 5, 2009

Labeling:
The sponsor submitted the most recent draft PI/PPI labeling on March 5, 2007 as email attachments and revised carton and container labels on January 26, 2007.

This NDA will be approved on draft labeling.

Advisory Committee Meeting
This application did not go before the Advisory Committee.

Project Manager's Summary
To my knowledge, there are no issues that might prevent taking regulatory action on this NDA.

John David, BSN, MS in HRM
Regulatory Health Project Manager

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/s/

John David
3/6/2007 03:29:38 PM
CSO

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; White Oak BLDG 22, Room 4447 Center for Drug Evaluation and Research

To: Norman Stockbridge, MD
Division of Cardiovascular and Renal Products
HFD-110

Through: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Denise V. Baugh, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: February 21, 2007

Subject: OSE Review 2007-263, Tekturna (Aliskiren) Tablets, 150 mg and 300 mg
NDA# 21-985

This memorandum is in response to a January 31, 2007 request from your division for a final review of the proprietary name, Tekturna. Additionally, revised container labels and carton labeling were provided for review and comment.

The proposed name, Tekturna, was found acceptable in OSE Review 2006-674 (dated November 17, 2006). Since the initial review of Tekturna, DMETS identified the names Ketek, Phenytek, and Rilutek as names that have the potential to look similar to Tekturna. However, upon further analysis Ketek, Phenytek, and Rilutek will not be reviewed due to a lack of convincing orthographic similarities in addition to differentiating product characteristics such as dosage form, frequency of administration, usual dose and/or indication for use. Thus, DMETS has no objections to the use of the proposed name, Tekturna.

In the review of the container labels and carton labeling, DMETS acknowledges that the sponsor has addressed our previous recommendations.

In summary, DMETS has no objections to the use of the proprietary name, Tekturna. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name, Tekturna, acceptable from a promotional perspective. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

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/s/

Denise Baugh
2/27/2007 08:24:10 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/27/2007 10:57:49 AM
DRUG SAFETY OFFICE REVIEWER

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and echnical Support (DMETS), HFD-420
WO22, RM 4447

FROM: John David
RHPM
Division of Cardiovascular and Renal Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
January 31, 2007	62,976	N/A	Carton/Container Labeling	January 26, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
aliskiren	Standard	renin inhibitor	February 28, 2007

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The submission of the revised carton/container labels are in the EDR (network path location is: \\CDSESUB1\N21985\N_000\2007-01-26) .

PDUFA DATE: 3/13/07.
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA IND 62,976
HFD-110/Division File
HFD-110/RPM
HFD-110/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
hn David, Project Manager 301-796-1059	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

John David
1/31/2007 01:53:50 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-985

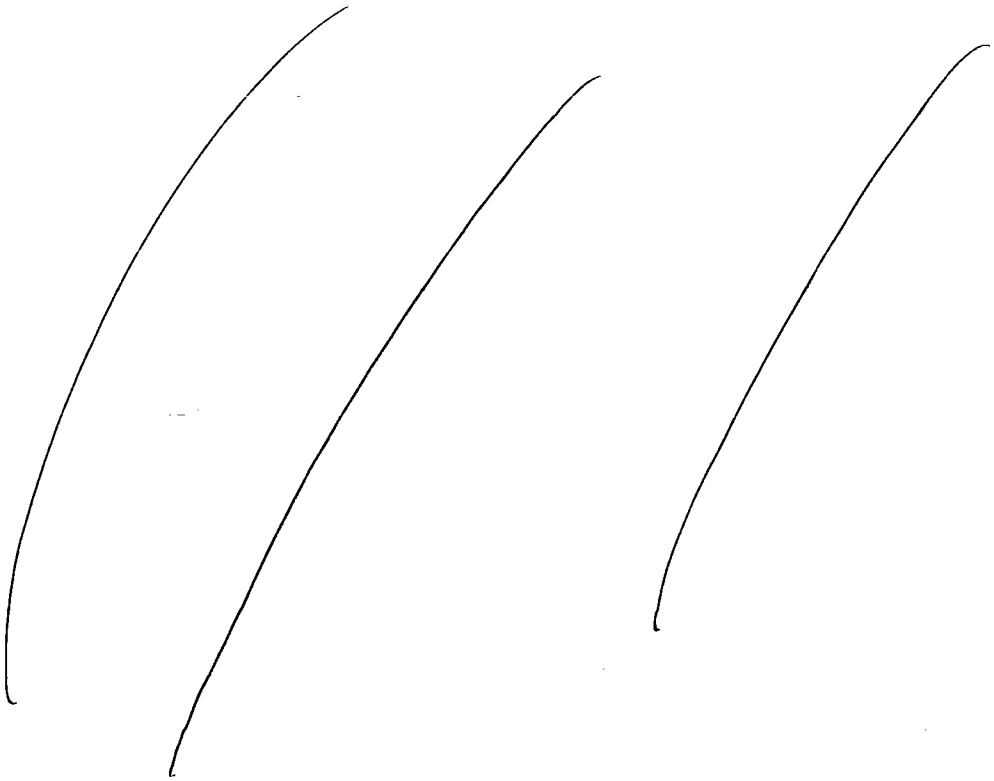
Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
Assistant Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

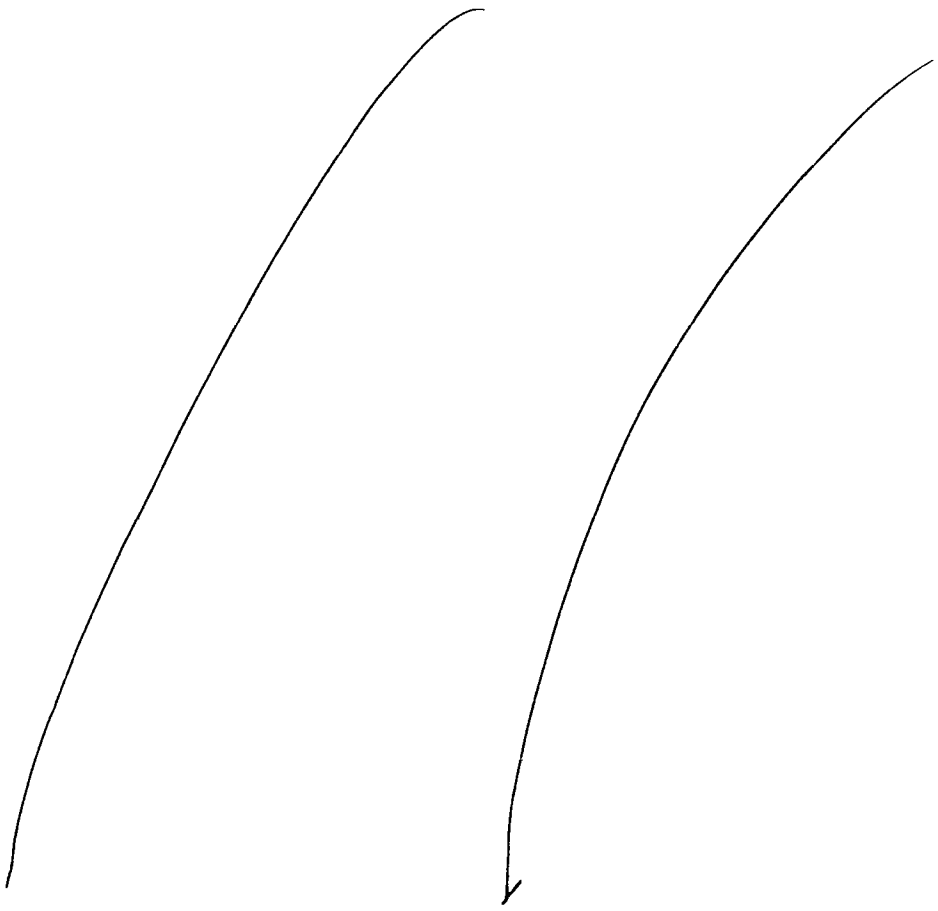
Dear Dr. Dickerson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tekturna (aliskiren) 150 mg and 300 mg tablets.

We also refer to your October 17, 2006 and November 3, 2006 submissions, containing updated carton and container labeling, proposed package insert, annotated package insert, and proposed patient package insert (PPI).

We have reviewed the referenced material and have the following comments and recommendations.





If you have any questions, please call Mr. John David, Regulatory Health Project Manager, at (301) 796-1059.

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
1/16/2007 05:42:10 PM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: Robert Justice, OND/OODP/DDOP WO22, RM 2112, 10903 New Hampshire

FROM: CDR John David, RHPM, HFD-110

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/1506	62,976	21-985	See attacted	12/15/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Rasilez (aliskiren)	Goal date extended	Renin Inhibitor	1/15/07

NAME OF FIRM: Novartis Pharmaceuticals Corp.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please see the attached documents for NDA 21-985 Rasilez (aliskiren) and provide comments.
The application was submitted on 2/10/06 and the labeling, dated 2/13/06 can be located in the EDR.
The goal date was extended to 3/13/07.

Aliskiren is the first renin inhibitor submitted for approval for the treatment of hypertension. In general its activity appears similar to other inhibitors of the renin-angiotensin-aldosterone system, particularly ACE inhibitors, but it has one additional or more pronounced toxicity: diarrhea. Diarrhea rates in humans are increased about two-fold at the highest proposed to-be-marketed dosage (300 mg daily), 6-10 fold at 600 mg, and higher at the higher dosages tested in various Phase I and II studies. The diarrhea at the to-be-marketed dosages is not problematic by itself (few discontinuations) but rather because of concern that it may be a marker for carcinogenicity as suggested by the pre-clinical studies. Rodents and marmosets develop diarrhea with aliskiren administration and rodents (not clear for marmosets) develop colonic and small intestinal mucosal hyperplasia. In a 24-month rat carcinogenicity study one colonic adenoma and one adenocarcinoma were found in males at the highest dosage level. While these rates are not statistically different than those in historical controls, such tumors are rare (< 0.1%) in the rat strain used so confidence intervals are wide. In a 6-month CB6F1/Jic-TgrasH2 hemizygous mouse study four mice (one male and

three females) showed focal atypical hyperplasia at the highest dosage. While the CAC did not judge that these findings justified disapproval, we remain concerned.

The sponsor apparently was concerned enough to propose and conduct a study with colonoscopic biopsies in 30 healthy volunteers pre- and post-eight-week treatment with aliskiren 300 mg daily or placebo (2:1 aliskiren:placebo). Because the sponsor submitted the preliminary results for this study in December, we considered this to be a major amendment to the NDA and extended the user fee goal date until March 13, 2007. While the sponsor claims that no hyperplasia was detected in this study, we have questions for you about the potential usefulness of special studies (e.g, Ki 67, PCNA) that the sponsor planned but is now saying will not be completed before the new goal date. We would also appreciate your advice and recommendations on some other issues related to the potential of aliskiren for carcinogenicity.

Before detailing our specific questions, we provide the following orientation to this submission because it is a complex submission: All of the sponsor's submissions (with the exception of the actual slides from the biopsy study, which you may review if you wish) are found in the EDR under NDA 021985. There were multiple supplementary submissions, so we have attached an Acrobat PDF file with a table describing briefly each submission. We have highlighted on the table the submissions most pertinent to this consult. The clinical, pharmtox, and statistical carcinogenicity review and the CAC minutes are available in DFS. We have also attached another Acrobat PDF file with the most pertinent excerpts from the pre-clinical studies and a recent sponsor's summary of GI safety that we could not find in the EDR.

Please answer the following questions:

1. The sponsor has planned special studies (Ki 67, PCNA, bcl-2) of the biopsy specimens (although the sponsor is now saying that their results will not be available prior to the new user fee goal date).
    a. How valid and useful are these special studies?
    b. Would you base a decision for non-approval on their results?
    c. Do you recommend delaying the decision for approval until their results are known?
    d. Do you consider one of them to be preferred?
    e. If you consider one of more of them to be useful, can you provide references validating their usefulness?
    f. Are there any other analyses that are preferable that can be performed on preserved tissue?
2. The sponsor developed scores for hyperplasia and mitoses upon which the sponsor is basing its claim that hyperplasia was not found in this study.
    a. Do you judge the sponsor's scores to be useful?
    b. Are you aware of any validated scores for hyperplasia?
    c. Can you suggest any alternatives?
3. We did request and obtain the slides from the colonic biopsy study and we have pathologists on our staff that will examine at least a sample of them.
    a. Do you have any other recommendations for analyzing the colonic biopsy study?
    b. Should we consider requesting one of the FDA laboratories to perform Ki 67 or PCNA assays from tissue blocks or unstained slides obtained from the sponsor?
4. The completed colonic biopsy study used the highest proposed to-be marketed dosage and its duration exceeded the earliest times at which hyperplasia was detected in rats.
    a. Do you judge that this study, if negative, will adequately exclude a risk of increased rates of colon cancer in man?
    b. If not, do you have any recommendations for further studies?
5. The sponsor is planning large cardiovascular outcome studies (about [redacted] persons exposure years apiece for both aliskiren and control) and will monitor cancer rates in those studies.
    a. Do you have any recommendations for monitoring in those studies?
    b. Would you recommend any other post-marketing studies or other commitments?

If you have any questions about this consult, please call Dr. Marciniak at 6-1118.

Thank you!

SIGNATURE OF REQUESTER John David	METHOD OF DELIVERY (Check one) X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Aliskiren NDA 021985 Submissions	
Date	**Description**
2006-02-10	Initial submission
2006-03-13	AE listings
2006-03-14	Study numbers & titles; biopharm methods
2006-03-17	SAE reports
2006-03-31	Biopharm navigation
2006-04-03	Biopharm reports
2006-04-04	Biopharm navigation
2006-04-05	Biopharm reports
2006-04-19	Clinical diarrhea, GI questions
2006-04-19	Biopharm info
2006-05-02	Pharmtox question
2006-06-13	120 day safety update
2006-06-22	CK rise case narrative & CRF - 1 case
2006-06-27	Pharmtox
2006-06-28	Patient package insert
2006-07-05	Chemistry
2006-07-06	Drop CRFs for 2203
2006-07-11	Chemisty
2006-08-01	Drop CRFs for other studies
2006-08-14	CRFs for edema, CK rise, other
2006-08-16	Valsartan combo study question
2006-08-31	Pharmtox question (historical control rate for rat colon adenoca)
2006-09-15	Study 2308 CRFs
2006-09-26	Possible stroke CRFs, Study 2208 SAS data sets
2006-09-28	Study 2327 partial results
2006-10-04	Study 2306 report & data plus other responses
2006-10-05	Safety update with Studies report & data), and 2304, 2323E1 (data)
2006-10-06	Stroke summary & biopharm responses
2006-10-13	Stability data
2006-10-17	Tekturna tradename change & labeling responses
2006-10-23	Brainstem strokes, CK rise, intrasubject variability
2006-10-25B	Chemistry
2006-10-25B	Additional safety update
2006-10-26	Mechanism of action explanation (no new data)
2006-11-02	Study report for the oral embryo-fetal development study in rabbits
2006-11-03	Elevated CK CRFs
2006-11-03A	Tekturna labeling
2006-11-07	Rat & human mucosal & fecal aliskiren levels
2006-11-09	
2006-11-15	Dose-response modeling
2006-11-16	CMC quality responses
2006-11-17	Treatment durations by treatment group
2006-11-21	Treatment start and end dates in SAS files
2006-11-29	Response to question on hygroscopic tablets & stability
2006-11-30	Dose-response modeling in elderly
2006-12-01	More dose-response modeling
[redacted]	[redacted]
[redacted]	[redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-985

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
Assistant Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

Please refer to your February 10, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tekturna (aliskiren) 150 mg and 300 mg Tablets.

On December 4, 2006, we received your December 4, 2006 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is March 13, 2007.

If you have any questions, please call Mr. John David, Regulatory Health Project Manager, at (301) 796-1059.

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
12/12/2006 01:39:19 PM

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

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

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

Transmitted via email:	kimberly.dickerson@novartis.com
Attention:	Kimberly Dickerson, Pharm.D.
Company Name:	Novartis Pharmaceuticals Corporation
Phone:	862-778-4576
Subject:	NDA 21-985 Regulatory Tcon Meeting Minutes
Date:	
Pages including this sheet:	

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

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

Minutes of a telecon between Novartis Pharmaceuticals Corporation and the FDA Division of Cardiovascular and Renal Products

Sponsor:	Novartis Pharmaceuticals Corporation
Drug:	Tekturna (aliskiren)
NDA:	21-985
Date of request:	November 20, 2006 (requested by FDA)
Date of meeting:	November 27, 2006
Time:	4:30 – 5 pm
Type/Classification:	C/Guidance
Meeting Chair:	Robert Temple, M.D.
Meeting recorder:	John David

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation I, HFD-101
Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products, HFD-110
Ellis Unger, M.D.	Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Gowra Jagadeesh, Ph.D.	Pharmacologist, HFD-110
Ana Szarfman, M.D.	Medical Officer, HFD-110
Xavier Ysern, Ph.D.	Chemist, HFD-810
Rajnikanth Madabushi, Ph.D	Pharmacometrics Reviewer, HFD-580
Monika Houstoun, Pharm.D.	Safety Evaluator (SE), Division of Drug Risk Evaluation (HFD-430)
Sammie Beam, R.Ph.	Project manager, Office of Surveillance and Epidemiology
Glady Singh	Consultant, Booz-Allen
John David	Regulatory Health Project Manager, HFD-110

Novartis Pharmaceuticals Corporation Participants:

Phillip Bentley, Ph.D.	Vice President & Global Head, Safety, Profiling & Assessment
Adrian Birch	Vice President, Drug Regulatory Affairs
Christopher Bush, Ph.D.	Sr. Associate Director, Biostatistics
Yann Tong Chiang, Ph.D.	Director, Biostatistics
Kimberly Dickerson, Pharm.D.	Associate Director, Drug Regulatory Affairs
William Dole, M.D.	Global Head, Exploratory Clinical Development
Mathieu Ghadnafar, M.D.	Global Brand Medical Director, Clinical Development and Medical Affairs
Glenn Gormley, M.D.	Global Head, US Clinical Development and Medical Affairs
Mathias Hukkelhoven, Ph.D.	Global Head, Drug Regulatory Affairs
Venkataswar Jarugula, Ph.D.	CVM, TA Head, Pharmacokinetics, ED-DMPK
Yatindra Joshi PhD, MBA	Vice President, Pharmaceutical & Analytical Development
Deborah Keefe, M.D.	Senior Director, Clinical Development and Medical Affairs
Daniel Lapadula	Vice President, Toxicology, Safety Profiling and Assessment
Marty Lefkowitz, M.D.	Executive Director, US Clinical Development and Medical Affairs
Elizabeth McCartney	Group Head, US Liaison Activities, Regulatory CMC
Ameet Nathwani, M.D.	Global Head CVM, Clinical Development and Medical Affairs
Ian Nicholls, B.Sc.	Safety, Profiling & Assessment

John Orloff, M.D.	Global Head Regulatory Strategy, Drug Regulatory Affairs
Goonaseelan (Colin) Pillai Ph.D.	Global M&S Pharmacology Head
Andrew Satlin, M.D.	Vice President, Drug Regulatory Affairs
Barbara Warner, M.D.	Vice President, CVM TA Safety Leader

Background:
Novartis Pharmaceuticals Corporation submitted this NDA for Tekturna (aliskiren) Tablets for the treatment of hypertension. They indicated that aliskiren is the first renin inhibitor to demonstrate efficacy and safety in a hypertensive population and they consider aliskiren to be a significant new product for the treatment of hypertension. Aliskiren is formulated as 150- and 300-mg film-coated tablets for oral administration. The sponsor is proposing once-daily dosing.

Aliskiren (Tekturna) is an inhibitor of renin, the enzyme that converts angiotensinogen to angiotensin I in the first and rate-limiting step of the renin-angiotensin-aldosterone system (RAAS). ACEIs (angiotensin converting enzyme inhibitors) inhibit the conversion of angiotensin I to angiotensin II by ACE. ARBs (angiotensin receptor blocker) block the action of angiotensin II at its receptor. Eplerenone and spironolactone block the effects of aldosterone, whose release is stimulated by angiotensin II.

Aliskiren has been evaluated for hypertension in a large clinical development program including five randomized, double-blind, placebo-controlled studies, six other completed active-controlled, and a large, longer-term safety study, as well as smaller studies in hypertension and other indications, and additional on-going active-controlled and a placebo-controlled study that will yield further safety reports. The initial submission included efficacy and safety data on 3,958 patients given aliskiren in the placebo-controlled studies and a total of 6,398 patients given aliskiren in controlled studies and the long term safety study. Of these 6,398 patients 1,714 were exposed for at least six months and 1,236 for at least one year. The PDUFA goal date is December 13, 2006.

Introductions:

Discussions:

Dr. Temple discussed the following regulatory items with the sponsor:

1. Dr. Temple informed the sponsor that the Division will need to review the findings from the ongoing 30-patient colonic biopsy study before reaching a regulatory decision. The sponsor indicated that they can provide accelerated full study reports with datasets of the 30 patients in 7 days. Dr. Temple indicated that the submission of substantial data prior to the goal date will be considered a major amendment; therefore, the goal date would be extended by 3 months upon receipt of the data.
2. Dr. Temple inquired if the drug
3. Dr. Temple recommended
4. Dr. Stockbridge inquired if BID dosing was studied. The sponsor indicated that BID dosing was not studied due to the 41 hour half-life of the drug. Dr. Stockbridge proposed that the sponsor may want to look at a QD (300 mg) versus BID (150 mg) study as a way of avoiding diarrhea. The sponsor indicated that they would consider the study proposal.

5. Dr. Temple noted the starting dose of 75 mg for elderly patients had only a modest effect and indicated that more data would be needed. The sponsor acknowledged the modest dose response but noted that diarrhea was more of an issue in elderly patients. The sponsor believes that 150 mg should be the starting dose based on the diarrhea and the 2 mm Hg systolic BP difference and they noted no changes between 75 mg and 150 mg doses. Dr. Marciniak indicated that the concern is diarrhea in the elderly with relatively flat dose-response through 300 mg. He questioned why the data show cases of diarrhea in the $\geq$ 65-year group, but the model showed essentially zero incidence over the dose range placebo to 300 mg. The sponsor said that the reason for this is the modeling technique over-weighted the zero incidence data-points in some treatment arms within the 6 studies that were pooled in this analysis. The sponsor

The sponsor noted that aliskiren is a competitive inhibitor of renin but that it takes time (4-5 weeks) for the full effect to be seen and they are continuing to study the inhibition. They noted that they do not know if it has effects on ACEs

Meeting recorder: _____
John David

Meeting concurrence: _____
Robert Temple, M.D.

Draft: 11/28/06
Final: 12/11/06

RD:
Ysern 11/30/06
Szarfman 12/1/06
Madabushi 12/1/06
Jagadeesh 12/1/06
Houstoun 12/1/06
Fromm 12/5/06
Marciniak 12/1/06
Unger 12/4/06
Stockbridge 12/7/06
Temple 12/8/06

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/s/

Robert Temple
12/11/2006 06:44:05 PM

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2 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-985

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
Assistant Director, Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

Please refer to your February 10, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tekturna (aliskeren) 150 mg and 300 mg tablets.

We also refer to your submission dated December 4, 2006 regarding the final report for Study No. SPP100A2103 ("Double-blind, placebo-controlled, randomized, parallel group, multi-center study to assess the effects on the colon mucosa of a daily dose of aliskiren 300mg administered orally for 8 weeks in healthy volunteers").

We are reviewing the Clinical 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.

Please provide the following documentation and materials:

1. Copies of all endoscopy reports, dictated procedure notes (as described in the protocol), biopsy reports, and all other documents with clinical or histopathologic information collected on the study subjects regardless of whether they are labeled case report forms.
2. Duplicate biopsy slides for all biopsies. We will return all biopsy slides to you upon completion of our review. If duplicates are not available, we would like to discuss with you how our review of the biopsy slides can be conducted.
3. Copies of all photographs specified by the protocol:
    a. Photographs of "anything noted as a distinct visual abnormality by the colonoscopist on Day 56 will be photographed, verbally described, and biopsied (as at least 2 additional biopsies) for clinical evaluation."
    b. Photographs of "the most proximal extent reached will be used to document the level of insertion, including ileal cecal valve where possible (as a quality parameter)."

Please answer the following questions and provide the requested documentation:

1. You use a hyperplasia score and a mitosis score for your primary analyses. Please describe how these scores were developed and validated. Provide any documentation on the chronology of the development and implementation.
2. The protocol specifies that validated grading systems for inflammation and hyperplasia will be used. Please provide the results for the validated grading system for inflammation. Please describe how the grading system was developed and validated. Provide any documentation on the chronology of the development and implementation.

3. The protocol states that similar evaluation will be conducted of mucosal biopsy tissue appropriately stained to demonstrate inflammatory cells, sections will be scored according to an accepted index and comparisons made between pre and post treatment to evaluate any change in histological parameters of inflammation. Please provide the results for the accepted index for inflammation. Please describe how the accepted index was developed and validated. Provide any documentation on the chronology of the development and implementation.
4. You exclude the terminal ileum biopsies from your analyses of the hyperplasia score and the mitosis score, but the protocol does not specify handling the biopsies from different areas differently except for the transverse colon biopsy specimens (to be frozen for future analyses). Please explain why you do not analyze the biopsies from the terminal ileum for hyperplasia and mitosis and, if the scores are not appropriate for the ileum specimens, why another approach was not used.
5. The protocol specifies obtaining the biopsies from normally appearing mucosa. It also specifies that anything noted as "a distinct visual abnormality" be biopsied. Were the latter biopsies included in your analyses? If not, why not? How are the latter biopsies identified in the SAS data sets? How was abnormally appearing mucosa handled? Was it consistently biopsied as a "distinct visual abnormality"?
6. The protocol specifies that the incidence of macroscopic inflammation of the terminal ileum and colon will be assessed by video colonoscopy and the corresponding photographs of any lesions will be graded using a validated scoring system. Please provide the results of these evaluations and how the scoring system was develop and validated. Provide any documentation on the chronology of the development and implementation.
7. The protocol describes that immunohistological tests will be used to evaluate markers of colon cell proliferation (Ki 67, PCNA) and apoptosis (bcl-2) and of response to inflammation. (e.g. myeloperoxidase for leukocytes) before and after treatment with study medication. Please provide the results of these tests.
8. The protocol describes that unblinding was possible locally at the sites — Did any unblinding occur during the conduct of the study? Please provide copies of the — documents from the sites.

We may have additional questions as our review of this study proceeds. If you have any questions, please call John David, Regulatory Health Project Manager, at (301) 796-1059.

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
12/8/2006 04:40:47 PM

MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; WO22, Mail Stop 4447 Center for Drug Evaluation and Research

To: Norman Stockbridge, MD
Division of Cardiovascular and Renal Products
HFD-110

Through: Linda Y. Kim-Jung, PharmD, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Loretta Holmes, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: November 17, 2006

Subject: DMETS Proprietary Name Review
Drug: Tekturna® (Aliskiren) Tablets, 150 mg and 300 mg
NDA#: 21-985 (IND# 62,976)
Sponsor: Novartis Pharmaceuticals Corporation

Review #: 2006-674

This memorandum is in response to an October 23, 2006 request from your Division for a re-review of the proprietary name, Tekturna (NDA 21-985, IND 62,976). Container labels, carton and package insert labeling were provided for review and comment.

In OSE Review 05-0264 dated January 12, 2006, the proposed proprietary name, Tekturna, was found acceptable. Since the January 12, 2006 review, DMETS has identified eight names (Testerone, Testred, Taxotere, Leukeran, Fertinex, Tikosyn, Taclonex, and Tekarin) as having the potential for look-alike confusion with Tekturna. However, these names were not reviewed further due to a lack of convincing look-alike similarities to Tekturna in addition to numerous differentiating product characteristics such as indication of use and strength. Additionally, Testerone, Taxotere, and Taclonex have a dosage form and route of administration that differs from Tekturna. Fertinex is a product that is no longer marketed and Tekarin is a foreign product available in Greece. Furthermore, the prescribing and dispensing of Tikosyn is limited to those prescribers and institutions who have completed the Tikosyn Education Program. Retail pharmacies must be enrolled in the Tikosyn In Pharmacy System program in order to dispense Tikosyn.

In review of the container, carton and package insert labeling of Tekturna, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement which may minimize potential user error.

B

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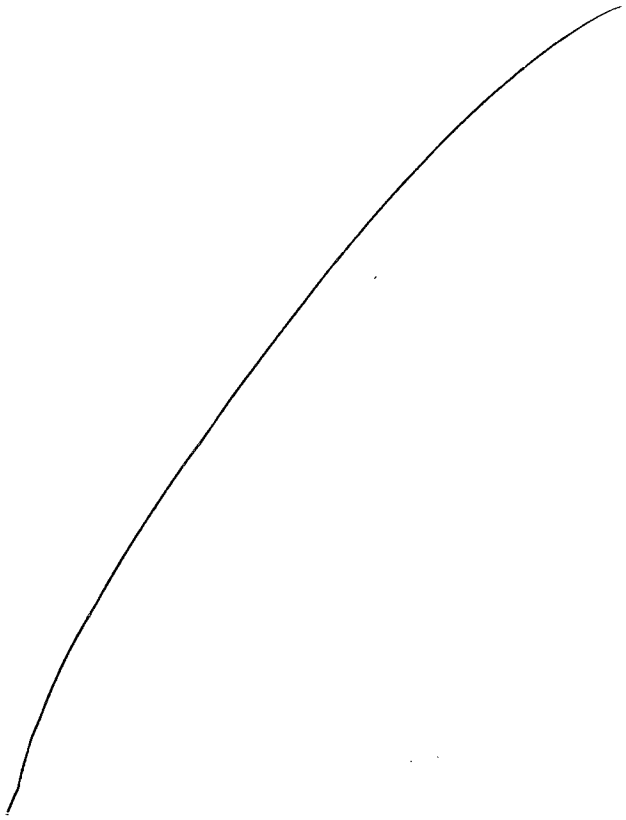
__✓__ Draft Labeling

_____ Deliberative Process



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G. PACKAGE INSERT

DMETS has no comments.

In summary, DMETS has no objections to the use of the proposed proprietary name, Tekturna. However, if approval of the NDA is delayed beyond 90 days from the signature date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from the signature date of this document. DMETS recommends implementation of the label and labeling recommendations as outlined above. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proprietary name, Tekturna, acceptable from a promotional perspective. If you have any questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

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/s/

Loretta Holmes
11/30/2006 12:44:10 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
11/30/2006 12:56:16 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
11/30/2006 01:39:00 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/30/2006 02:06:25 PM
DRUG SAFETY OFFICE REVIEWER

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

Sponsor Name:	Novartis Pharmaceuticals Corporation
Application Number:	NDA 21-985
Product Name:	Tekturna (SPP 100 aliskiren 150/350 mg film coated tablets)
Meeting Type:	Type C
Meeting Category:	CMC IR Letter Discussion
Meeting Date and Time:	November 13, 2006
Meeting Location:	Teleconference
Received Briefing Package	N/A
Meeting Requestor:	Xavier Ysern, Ph.D.
Meeting Chair:	Ramesh Sood, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES:

Division of Pre-Marketing Assessment I

Ramesh Sood, Ph.D.; Branch Chief
Kasturi Srinivasachar, Ph.D.; Pharmaceutical Assessment Lead
Xavier Ysern, Ph.D.; Review Chemist
Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

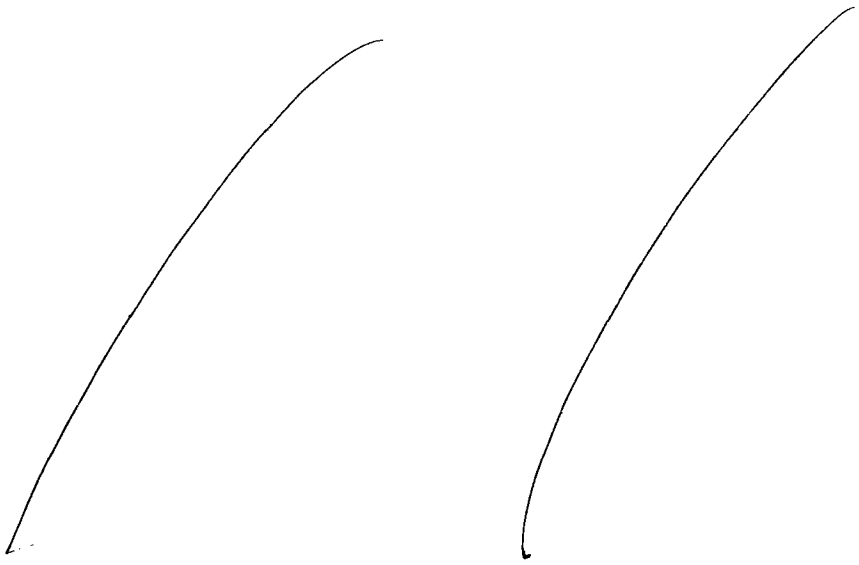
EXTERNAL ATTENDEES:

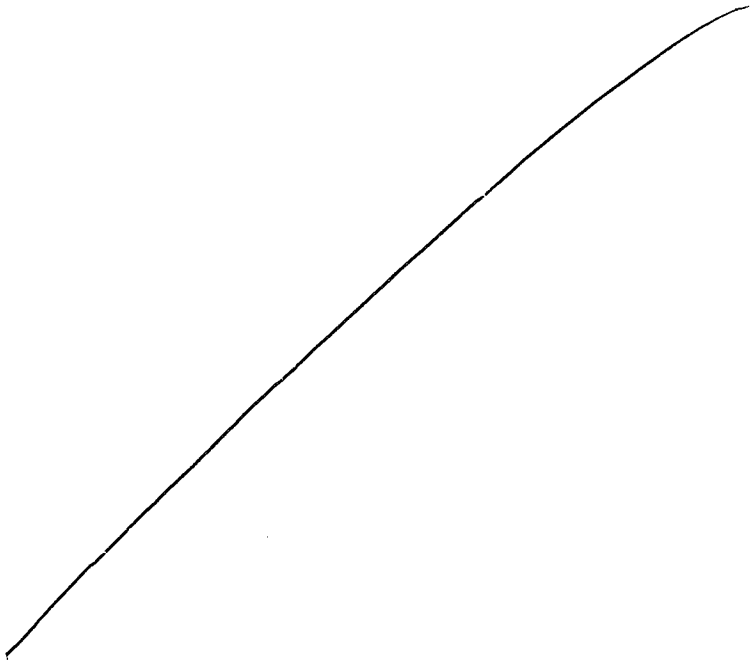
Adrian Birch, Vice President, Drug Regulatory Affairs
Herbert Gehrhardt, Ph.D., Project Team Leader, Chemical Operations
Stefan Hirsch, Ph.D., Technical Project Leader, Pharmaceutical and Analytical Development
Mathias Hukkelhoven, Ph.D., Global Head, Drug Regulatory Affairs
Yatindra Joshi, Ph.D., M.B.A., Vice President, Pharmaceutical and Analytical Development
Sharon Kawam, Project Management
Elizabeth McCartney, Group Head, US Liaison Activities, Global Regulatory CMC
Hans-Peter Mennet, Ph.D., Project Team leader, Pharmaceutical Operations
Daniel Wasmuth, Ph.D., Technical Project Leader, Chemical and Analytical Development

BACKGROUND

Novartis Pharmaceuticals Corporation (Novartis) has submitted NDA 21-985 for SPP100, aliskiren (Tekturna) 150 mg and 300 mg film coated tablets, proposed for the treatment of hypertension alone and in combination with other anti-hypertensive agents. On October 27, 2006, FDA issued a CMC information request letter that contained 4 comments and information requests (See Discussion points 2.1 to 2.4). On November 2, 2006, received November 3, 2006, Novartis responded to FDA's October 27, 2006 information request letter. FDA requested a teleconference to discuss and clarify Novartis' responses. FDA and Novartis met via teleconference on November 13, 2006.

2.0 DISCUSSION





3.0 ISSUES REQUIRING FURTHER DISCUSSION:

There were no issues requiring further discussion.

4.0 ACTION ITEMS:

Novartis committed to provide the following information as an amendment to the NDA:

- The acceptance criteria for _____ would be based on existing observations from the Certificate of Analysis obtained from their supplier.
- A post marketing commitment in the application to develop and implement a test method and acceptance criteria for the assay of _____

- A commitment that [redacted]
- A commitment that [redacted]
- A specification for assay of [redacted] based on data from existing batches, and scientific justification for the acceptance criteria.
- Revised acceptance limits for residual solvents, and total impurities based on the levels observed in existing batches, and scientific justification for the acceptance criteria.
- A c ommitment to re-evaluate the [redacted] acceptance limit as more commercial data become available.

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 distributed or presented during the teleconference to be included in the meeting minutes.

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/s/

Ramesh Sood
11/22/2006 03:29:09 PM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
WO22, RM 4447

FROM: John David
RHPM
Division of Cardiovascular and Renal Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 23, 2006	62,976	N/A	Labeling	October 23, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
aliskiren	Standard	renin inhibitor	November 23, 2006

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The Sponsor has selected their 2nd choice TEKTURNA (Indication: hypertension) The submission of the revise carton/container labels are in the EDR (network path location is: \\CDSESUB1\N21985\N_000\2006-10-17) . Please see the revised proposed labeling attached (the line numbered version was also forwarded to the reviewer.

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7 Draft Labeling

_____ Deliberative Process

PDUFA DATE: 12/13/06.
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA IND 62,976
HFD-110/Division File
HFD-110/RPM
HFD-110/Reviewers and Team Leaders

AME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
John David, Project Manager 301-796-1059	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

John David
10/23/2006 02:24:04 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-985 Supplement # 000 Efficacy Supplement Type SE- N/A

Trade Name: Rasilez
Established Name: aliskiren

Strengths: 150 mg, 300 mg Tablet

Applicant: Novartis Pharmaceuticals Corporation
Agent for Applicant: N/A

Date of Application: February 10, 2006
Date of Receipt: February 13, 2006
Date clock started after UN: N/A
Date of Filing Meeting: March 24, 2006
Filing Date: April 14, 2006
Action Goal Date (optional): December 13, 2006 User Fee Goal Date: December 13, 2006

Indication(s) requested: treatment of hypertension, alone or in combination with other anti-hypertensive agents

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication*

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☐ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? Everything except for all forms and certifications requiring official signatures.

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☐ NO ☒

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  ***NOTE:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) 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 . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 62,976

- End-of-Phase 2 Meeting(s)? Date(s) 7/28/04 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 4/26/05 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐