

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 24, 2006

BACKGROUND: Novartis Pharmaceuticals Corporation submitted this NDA for Rasilez (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.

The Division granted a deferral of pediatric assessments in the original New Drug Application for aliskiren (refer to IND 62, 976 letter dated August 26, 2004).

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Ellis Unger, M.D.	Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Lydia Velazquez, Pharm.D.	Clinical Pharmacology/Biopharmaceutics, HFD-860
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Gowra Jagadeesh, Ph.D.	Pharmacologist, HFD-110
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-110
Xavier Ysern, Ph.D.	Chemist, HFD-
Steven Bai, Ph.D.	Statistician, HFD-710
Ququan Liu, Ph.D.	Statistician, HFD-710
Arpita Shah, Pharm.D.	Post-Doctoral Fellow
Kavita Johal, PharmD	Post-Doctoral Fellow
Edward Fromm	Chief, Project Management Staff, HFD-110
John David	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS (including those not present at filing meeting):

<u>Discipline</u>	<u>Reviewer</u>	<u>Review Due</u>
Medical:	Thomas Marciniak, M.D.	October 15, 2006
Statistical:	Steven Bai, Ph.D.	October 15, 2006
Pharmacology:	Gowra Jagadeesh, Ph.D.	September 30, 2006
Statistical Pharmacology:	Ququan Liu, Ph.D.	June 26, 2006
Chemistry:	Xavier Ysern, Ph.D.	August 30, 2006
Environmental Assessment (if needed):		
Biopharmaceutical:	Lydia Velazquez, Pharm.D.	October 15, 2006
Microbiology, sterility:		
Microbiology, clinical (for antimicrobial products only):		
DSI:		
Regulatory Project Management:	John David	
DDMAC:	Lisa Hubbard	

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site inspection needed? YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. inspection needed? YES NO

PHARMACOLOGY N/A FILE REFUSE TO FILE

- GLP inspection needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

John David
Regulatory Project Manager, HFD-110

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ON ORIGINAL**

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Trade Secret / Confidential

Draft Labeling

Deliberative Process

Executive CAC

Date of Meeting: September 5, 2006

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Joseph Contrera, Ph.D., OPS, Member
Abby Jacobs, Ph.D., OND IO, Member
Charles Resnick, Ph.D., DCaRP, Team Leader
Gowra Jagadeesh, Ph.D., DCaRP, Presenting Reviewer

Author of Draft: Gowra Jagadeesh, Ph.D.

The following brief summary reflects the Division's presentation as well as the Committee's discussion and its recommendations. Detailed study information can be found in Dr. Jagadeesh's review.

NDA #: 21-985
Drug Name: Aliskiren hemifumarate
Sponsor: Novartis Pharmaceutical Corporation

Background: Aliskiren is a non-peptide renin inhibitor (first in class) proposed for the treatment of hypertension. The carcinogenicity study protocols for both the rat and mouse were previously approved by the Executive CAC.

Rat Carcinogenicity Study

Dietary administration of aliskiren hemifumarate to Wistar Hannover rats for up to 104 weeks at dose levels of up to 1500 mg aliskiren/kg/day was associated with decreased mortality for both sexes. At week 91, there were at least 48 males and 46 females alive in each group, demonstrating that sufficient number of animals lived long enough to have been adequately exposed to the test substance. Large decreases in body weight gain for both sexes at 750 or more mg/kg/day (18 to 47% relative to concurrent control, dose-related and statistically significant as early as week 26) suggest the attainment of an MTD.

No aliskiren-induced effects on the number of tumor-bearing animals, number of animals bearing benign tumors, number of animals bearing malignant tumors or number of animals bearing multiple tumors were apparent for either sex of rats that were killed or died during the treatment period, or killed at term. Although not statistically significant, a colonic adenoma was found in one male and a cecal adenocarcinoma was found in another male (both historically rare tumors, <0.1%), at 1500 mg/kg/day. The FDA analysis showed no statistically significant positive trend or difference from control for any tumor type for either male or female rats.

Mouse Carcinogenicity Study

Dietary administration of aliskiren hemifumarate to CB6F1/Jic-TgrasH2 hemizygous mice for 26 weeks at dose levels of up to 1500 mg aliskiren/kg/day did not elicit clinical signs of toxicity. The FDA analysis showed a statistically significant increase in mortality for males at 1500

mg/kg/day. Significantly reduced body weight gain relative to control was noted for males at all doses (dose-related) and for females in the high dose group.

The incidence and types of neoplastic findings noted with aliskiren hemifumarate-treated groups were similar to the incidence and types of spontaneous tumors reported for concurrent and historical control Tg-rasH2 transgenic mice. In contrast, the focal atypical hyperplasia (a pre-neoplastic finding) noted in the colons of high dose animals (1 male and 3 females) is not a common spontaneous lesion. Although hemangiomas and/or hemangiosarcomas were more frequent in treated males and females, the distribution showed no dose-dependency and no statistically significant difference from concurrent control. Furthermore, the incidence of these tumors (up to 13%) is within the range reported for untreated CB6F1-TgrasH2 female mice of this age (up to 20% in studies submitted to CDER) and, thus, the occurrence of these tumors was not considered to be treatment-related. The sponsor concludes that there were no differences in neoplastic findings between control and aliskiren hemifumarate-treated male and female groups. The FDA/CDER analysis also showed no evidence of aliskiren-related tumorigenicity for male or female mice. Positive control mice treated with methyl nitrosourea were characterized by a high incidence of tumors (malignant lymphoma, squamous cell carcinoma or papilloma in the forestomach or skin and adenoma in the lung in both sexes).

Executive CAC Recommendations and Conclusions:

Rats

- The Committee concluded that the study was adequate, noting prior Executive CAC concurrence on doses.
- The Committee concurred that the study was negative for drug-related neoplasms.

Mice

- The Committee concluded that the study was adequate, noting prior Executive CAC concurrence on doses.
- The Committee concurred that the study was negative for drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DCaRP
/C.Resnick, DCaRP
/G.Jagadeesh, DCaRP
/John David, DCaRP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
9/7/2006 09:53:40 AM



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 Rasilez (aliskeren) 150 mg and 300 mg tablets.

We also refer to your August 16, 2006 submission, containing answers to questions from the "Response to Health Authority Questions" dated August 15, 2006.

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

The submission of Study 2327 will not be interpreted as a major amendment and will not reset the PDUFA deadline. We will need the SAS datasets and the CRFs (all forms, including SAE worksheets, etc.). However, while we will not reset the PDUFA deadline, complete evaluation of this submission may not be possible prior to the current PDUFA deadline due to the submission's incomplete nature and late submission date.

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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this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
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CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; White Oak 22, Mail Stop 4447)**

DATE RECEIVED: December 5, 2005	DESIRED COMPLETION DATE: February 6, 2006	OSE REVIEW #: 05-0263 and 05-0264
DATE OF DOCUMENTS: February 10, 2006	PDUFA: December 13, 2006	

TO: Norman Stockbridge, M.D.
Director, Division of Cardiovascular and Renal Products
HFD-110

THROUGH: Linda Kim-Jung, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: **Rasilez (primary)**
Tekturna (secondary)
(Aliskiren Tablets)
150 mg and 300 mg

NDA#: 21-985 (IND # 62,976)

NDA SPONSOR: Novartis Pharmaceuticals Corporation

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Rasilez. However, DMETS has no objections to the use of the proprietary name, Tekturna. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary names, Rasilez and Tekturna, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
HFD-420; White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 12, 2006

NDA#: 21-985

NAME OF DRUG: Rasilez (primary)
Tekturna (secondary)
(Aliskiren Tablets)
150 mg and 300 mg

NDA HOLDER: Novartis Pharmaceuticals Corporation

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardiovascular and Renal Products (HFD-110), for assessment of the proprietary names, Rasilez and Tekturna, regarding potential name confusion with other proprietary or established drug names. Container labels, carton, and insert labeling were provided for review and comment. Additionally, Novartis has submitted trademark reports from the _____, for the proposed proprietary names, Rasilez and Tekturna, for review and comment.

PRODUCT INFORMATION

Rasilez/Tekturna (Aliskiren Tablets) is a non-peptide renin inhibitor and is proposed for the treatment of hypertension as monotherapy or in combination with other anti-hypertensive agents. The sponsor has proposed a 150 mg starting dose and for patients whose blood pressure is not adequately controlled, a 300 mg maximum dose, administered as an oral tablet taken once daily. Both the 150 mg and 300 mg strengths will be packaged in bottles of 30 or 90 tablets and in unit dose blister packages of 100 tablets (10 strips of 10 tablets).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Rasilez/Tekturna to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, for each name DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, Rasilez and Tekturna. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC has no objections to the tradenames, Rasilez or Tekturna, from a promotional perspective.
2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Rasilez. Independent review identified two additional names, Reyataz and Rozerem, to have significant phonetic or orthographic similarity to Rasilez. These products are listed in Table 1 (see pages 4-5), along with the dosage forms available and usual dosage.
3. DMETS noted that when pronounced, Rasilez sounds like it ends in the word "less", but we do not consider this to be a potential safety risk.
4. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Tekturna. These products are listed in Table 2 (see page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

⁴ Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified for Rasilez

Product Name	Dosage form(s), Established name	Usual adult dose	Other
Rasilez	Atiskiren Tablets: 150 mg, 300 mg	150 mg orally once daily for starting dose Maximum dose is 300 mg daily	N/A
Rezulin	Troglitazone Tablets: 200 mg, 300 mg, 400 mg <i>Discontinued product</i>	One tablet once daily with a meal.	SA
Restasis	Cyclosporine Emulsion, ophthalmic: 0.05% 32 x 0.4 ml vials	Instill one drop into affected eye(s) twice daily approximately 12 hours apart. Artificial tears may be used concurrently, allowing a 15 minute interval between administrations.	LA
Reyataz	Atazanavir Capsules: 100 mg, 150 mg, 200 mg	<u>Protease inhibitor experienced patients:</u> 300 mg orally once daily with a light meal plus ritonavir (100 mg once daily). <u>Antiretroviral treatment naive patients:</u> 400 mg orally once daily with a light meal	LA/SA
Rozerem	Ramelteon Tablets: 8 mg	8 mg orally taken within 30 minutes of going to bed. Rozerem should not be taken with or immediately after a high fat meal.	LA
<p>*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike) ***Name pending approval. Not FOI releaseable.</p>			

Table 2: Potential Sound-Alike/Look-Alike Names Identified for Tekturna

Product Name	Dosage form(s), Established name	Usual adult dose	Other
Tekturna	Atiskiren Tablets: 150 mg, 300 mg	150 mg orally once daily for starting dose Maximum dose is 300 mg daily	N/A
Sanctura	Trospium Chloride Tablets: 20 mg	Adults: 20 mg PO twice daily. May titrate downward to 20 mg PO once daily at bedtime if anticholinergic side effects are intolerable. NOTE: Trospium is given 1 hour before meals or on empty stomach.	SA/LA
Eterna Bella Anti Wrinkle Cream <i>Non-prescription</i>	Pregnenolone Acetate Cream: 0.5% Anti-wrinkle/anti-aging cream	Apply to the face and neck twice daily	SA
Revlon Eterna 27 Cream <i>Non-prescription</i>	Active ingredient and strength not identified Anti-wrinkle/anti-aging cream	Cleanse skin thoroughly. Then apply 1/4 to 1/2 teaspoon of cream to throat, neck and face. Massage with firm upward strokes until cream disappears. Leave on overnight.	SA
<p>*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike) ***Name pending approval. Not FOI releaseable.</p>			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Separate separate studies were conducted within the Centers of the FDA for each proposed proprietary name to determine the degree of confusion of Rasilez/Tekturma with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each name study employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Rasilez or Tekturma (see pages 5-6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

a. Rasilez

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p style="text-align: center;">Rasilez 150mg #15 — 1 tab QD</p>	<p>“Rasilez 150 mg, dispense #15, take one tablet daily”</p>
<p>Inpatient RX:</p> <p style="text-align: center;">Rasilez 150mg 1tab QD</p>	

b. Results for Rasilez:

Three respondents in the verbal study interpreted Rasilez as “Rezulez” which is similar to “Rezulin”, a prescription diabetic medication that was removed from the market in 2000. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, Rasilez. See Appendix A (page 13) for the complete listing of interpretations from the verbal and written studies.

c. Tekturna

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p style="text-align: center;">Tekturna 150mg # 30 i QD</p>	<p style="text-align: center;">“Tekturna 150 mg, quantity of 30, take one tablet daily”</p>
<p>Inpatient RX:</p> <hr/> <p style="text-align: center;">Tekturna 150mg i take daily</p>	

d. Results for Tekturna:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. One respondent in the verbal study commented that “Ecterna (Comment: sounds like Eterna, a hormone-containing cosmetic, but unlikely to be dispensed for an oral product). The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Tekturna. See Appendix B (page 14) for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Rasilez Name Review

In reviewing the proprietary name, Rasilez, the primary concerns relating to look-alike and sound-alike confusion with Rasliez are Rezulin, Restasis, and . Similarly, through independent review two additional names, Reyataz and Rozerem, were also determined to have potential for confusion with Rasilez. DMETS also noted that when pronounced, Rasilez sounds like it ends in the word “less.” However, we do not consider this to be a potential safety risk.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, three respondents in the verbal study interpreted Rasilez as “Rezulez,” which is similar to “Rezulin”, a prescription diabetic medication that was removed from the market in 2000. Rezulin was removed from the market by the manufacturer due to the risk of liver toxicity, and is not likely to ever be marketed again in the United States. Therefore, Rezulin will not be considered further.

Upon review of Restasis, it was determined that this name lacked convincing look-alike/sound-alike similarities with Rasilez in addition to having numerous different product characteristics such as the product strength, indication for use, frequency of administration, route of administration, and dosage form. Considering these differences, the name Restasis will not be discussed further. Additionally, upon review of the name

not be reviewed further.

so it will

- a. Reyataz was identified as a name with similar sound and appearance to Rasilez. Reyataz is a currently marketed prescription antiretroviral protease inhibitor indicated for the treatment of human immunodeficiency virus (HIV-1) infection. Reyataz is taken at a dose of 300 mg (two 150 mg capsules) with 100 mg of ritonavir for therapy-experienced patients or 400 mg (two 200 mg capsules) for therapy-naïve patients, both taken orally once a day.

Reyataz and Rasilez have orthographic similarities including the same word length (7 letters), the same beginning letter 'R' and the same ending letter 'z'. The middle portion of the name '-asile-' in Rasilez may also look like the middle portion of the name '-eyata-' in Reyataz, especially if the dot in the letter "i" is left off or lacks prominence or if the letter "t" is not crossed.

Reyataz 300 mg po qd
Rasilez 300 mg po qd

The two names also sound similar due to the shared letters 'R' and 'z'. However, the middle portions of the names '-asile-' and '-eyeta-' may sound different. The letter 'a' in Rasilez is usually pronounced with a short letter 'a' whereas the letter 'e' in Reyataz are pronounced as a long 'a' sound. Additionally, the syllable '-il-' in Rasilez and the syllable '-ya-' in Reyataz are both pronounced with emphasis and sound different. Finally, the last syllable of each name sounds distinctly different (-lez vs. -taz). However, the two products share an overlapping strength (150 mg), dose (300 mg) and frequency of administration (once daily) which increases the potential for confusion. The Reyataz 300 mg dose should also be taken with 100 mg ritonavir and a light meal, but these additional directions for use may not always be included on a prescription. Nor will these drugs always be filled simultaneously or perhaps even at the same pharmacy.

DMETS has concerns regarding the look-alike similarities between these products should a prescription be written with the directions "300 mg orally once daily as directed". The two names look similar and the overlapping characteristics increase the potential for confusion. Thus, DMETS believes that the tradenames Reyataz and Rasilez should not co-exist in the marketplace.

- b. Rozerem was identified as a name with similar appearance to Rasilez. Rozerem is a prescription sleep aid and is taken as one 8 mg tablet within 30 minutes of bedtime. The two names share some orthographic similarities due to the shared beginning letter 'R'. However, the name Rasilez contains an upstroke from the letter 'l' which may help to differentiate the two names. Additionally, if the letters 'z' in Rasilez and Rozerem are scripted with a downstroke, it may help to further differentiate between the two names. However, if they are not scripted with a downstroke, it may not be a significant differentiating factor. The two names share a dosage form (tablet), route of administration (oral), and may share a dosing frequency (once daily). However, it is more likely that Rozerem prescriptions will specify "once daily at bedtime" or a reference to bedtime because Rozerem is a sleep aid which may help differentiate between the two

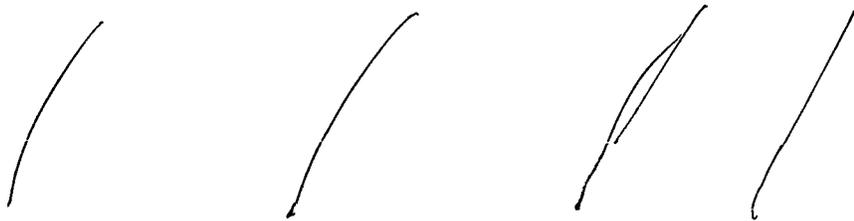
names. As Rozerem is available in one strength, prescriptions for Rozerem may be written without specifying a strength. However, prescriptions for Rasilez should specify which of the strengths (150 mg or 300 mg) is ordered, which may help to differentiate between the two names. Thus, orthographic differences along with the product strength will help to minimize the potential for confusion between the two drug products.

Rozerem
Rasilez

2. Tekturna Name Review

In reviewing the proprietary name, Tekturna, the primary concerns relating to look-alike and sound-alike confusion with Tekturna are Sanctura, Eterna, and —

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, one respondent in the verbal study commented that “Ecterna (Comment: sounds like Eterna. a hormone-containing cosmetic, but unlikely to be dispensed for an oral product). DMETS found two OTC products that contain “Eterna” in their names, Revlon’s “Eterna ‘27’ All-Day Moisture Cream” and “Eterna Bella Anti Wrinkle Cream.” Due to numerous different product characteristics such as the product dose, indication for use, frequency of administration, and route of administration, DMETS does not consider this to be a potential safety risk, therefore, Eterna will not be considered further. The majority of misinterpretations from the prescription analysis studies were misspelled/phonetic variations of the proposed name, Tekturna.



The final name, Sanctura, was identified as a name with similar sound and appearance to Tekturna. Sanctura is a non-specific antimuscarinic agent used orally in the treatment of overactive bladder. Sanctura is taken initially as 20 mg orally twice daily, although it may be titrated downward to 20 mg orally once a day. Sanctura should be taken one hour before meals or on an empty stomach.

Sanctura and Tektura share some orthographic similarities when scripted. The letter ‘n’ in Sanctura and the letter ‘k’ in Tekturna can look similar if the upstroke in the letter ‘k’ is not prominent (see page 8). Additionally, the endings for both names (-tura vs. -turna) can look nearly identical when scripted. However, the beginning letter for each name (S- vs. T-) looks different which may help to differentiate between the two names.

Sanctura Tekturna

The two names may also sound similar due to the similar endings. However, the letter 'n' in Tekturna is noticeable when spoken and may help to differentiate the two names. Additionally, the prefixes for each name (Sanc- vs. Tek-) sound different due to the long 'a' sound of the first letter a in Sanctura and the short 'e' sound (-eh-) in Tekturna which may help differentiate the two names.

Sanctura is available in one strength (20 mg) so the strength may not be specified on a prescription, whereas Tekturna has two strengths (150 mg and 300 mg) so a strength should be present on a prescription for Tekturna. The initial dosage frequency for Sanctura is twice daily, whereas Tekturna is dosed once a day. However, it is possible for the dose of Sanctura to be decreased to once a day administration if the side effects are intolerable. In this case, the presence of a strength on the Tekturna prescription may help differentiate it from a prescription for Sanctura. Thus, orthographic and phonetic differences along with the product strength will help to minimize the potential for confusion between the two drug products.

E. INDEPENDENT NAME ANALYSIS

1. Rasilez

The sponsor employed _____, to conduct an independent analysis of the proposed proprietary name, Rasilez. This analysis was forwarded to DMETS for review and comment. _____ employed a total of 42 pharmacists in the study. _____ analysis determined that overall, the proposed trademark RASILEZ has low vulnerability for look-alike and sound-alike confusion. Their responses are described below, along with DMETS response.

a. Table 1 – Look-alike names with potential for confusion

_____ did not identify any names that were identified by the respondents as having the potential for look-alike confusion when handwritten.

DMETS Response:

DMETS acknowledges _____ response. However, DMETS identified and evaluated the name Reyataz from a look-alike and sound-alike perspective in section IID of this review. We are unable to determine if the _____ group discussed Reyataz in their study. However, DMETS maintains that the names Rasilez and Reyataz should not co-exist in the marketplace, primarily due to look-alike similarity.

b. Table II – Sound-alike names with potential for confusion

_____ did not identify any names that were mentioned by the respondents as having the potential for sound-alike confusion.

DMETS Response:

DMETS acknowledges _____ response. However, DMETS identified and evaluated the name Reyataz from a look-alike and sound-alike perspective in section IID of this review. We are unable to determine if the _____ group discussed Reyataz in their study. However, DMETS maintains that the names Rasilez and Reyataz should not co-exist in the marketplace.

c. Table III – Medical terms with potential for confusion

_____ did not identify any medical terms that were mentioned by the respondents as having potential for confusion.

DMETS Response:

DMETS acknowledges _____ response. DMETS also did not identify any medical terms that were mentioned by respondents as having potential for confusion.

d. Table IV – Respondent’s suitability comments (rating) of proposed trademarks.

_____ identified the following remarks from the respondents: “-LEZ sounds like ‘less’ which is good when treating hypertension”.

DMETS Response:

DMETS also discussed the sound of “less” and does not consider this a potential safety risk. Furthermore, DDMAC found the name, Rasilez, acceptable from a promotional perspective.

e. Table V – FDA and USAN Regulatory Assessment

_____ presented evaluation criteria drawn from the paper _____

DMETS Response:

DMETS cannot comment on the regulatory assessment provided by _____. The paper quoted was published in _____ and is not currently used by DMETS to evaluate tradenames.

Conclusions:

DMETS does not concur with the _____ analysis summary of an overall low vulnerability of the name Rasilez. DMETS identified and evaluated the name Reyataz from a look-alike and sound-alike perspective in section IID of this review. We are unable to determine if the _____ group discussed Reyataz in their study. However, DMETS maintains that the names Rasilez and Reyataz should not co-exist in the marketplace for the reasons outlined in section C1a of this review.

2. Tekturna

The sponsor employed _____ to conduct an independent analysis of the proposed proprietary name, Tekturna. This analysis was forwarded to DMETS for review and comment. _____ employed a total of 42 pharmacists in the study. _____ analysis determined that overall, the proposed trademark TEKTURNA has low vulnerability for look-alike and sound-alike confusion. Their responses are described below, along with DMETS response.

a. Table I – Look-alike names with potential for confusion

_____ respondents identified the over-the-counter drug, Tetterine, as having the potential for look-alike confusion when handwritten.

DMETS Response:

DMETS acknowledges _____ response. Tetterine was not a name identified by DMETS. However, upon review of Tetterine, it was determined that this name lacked convincing look-alike/sound-alike similarities with Tekturna in addition to having numerous different product characteristics such as the product strength, indication for use, frequency of administration, route of administration, and dosage formulation ordered.

b. Table II – Sound-alike names with potential for confusion

_____ did not identify any names that were mentioned by the respondents as having the potential for sound-alike confusion.

DMETS Response:

DMETS acknowledges _____ response.

c. Table III – Medical terms with potential for confusion

_____ did not identify any medical terms that were mentioned by the respondents as having potential for confusion.

DMETS Response:

DMETS acknowledges _____ response. DMETS also did not identify any medical terms that were mentioned by respondents as having potential for confusion.

- d. Table IV – Respondent’s suitability comments (rating) of proposed trademarks.

_____ identified the following remarks from the respondents: “sounds like a technology term- ‘TEK’” and “sounds like ‘tech’”.

DMETS Response:

DMETS did not identify “tek” as being a problem with respect to it sounding like a technology term. However, upon discussion concerning the sound of “tek”, we do not consider this to be a potential safety risk. Furthermore, DDMAC found the name, Tekturna, acceptable from a promotional perspective.

- e. Table V – FDA and USAN Regulatory Assessment

_____ presented evaluation criteria drawn from the paper _____

DMETS Response:

DMETS cannot comment on the regulatory assessment provided by _____. The paper quoted was published in _____ and is not currently used by DMETS to evaluate tradenames.

Conclusions:

DMETS concurs with the _____ analysis summary of an overall low vulnerability of the name Tekturna. DMETS has no objection to the use of the proposed proprietary name, Tekturna.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Rasilez. In reviewing the proprietary name, the primary concerns related to look-alike or sound-alike confusion with Reyataz. However, DMETS has no objections to the use of the proprietary name, Tekturna.

Reyataz was identified as a name with similar sound and appearance to Rasilez. Reyataz is a currently marketed prescription antiretroviral protease inhibitor indicated for the treatment of human immunodeficiency virus (HIV-1) infection. Reyataz is taken at a dose of 300 mg (two 150 mg capsules) with 100 mg of ritonavir for therapy-experienced patients or 400 mg (two 200 mg capsules) for therapy-naïve patients, both taken orally once a day.

Reyataz and Rasilez have orthographic similarities including the same word length (7 letters), the same beginning letter ‘R’ and the same ending letter ‘z’. The middle portion of the name ‘-asile-’ in Rasilez

may also look like the middle portion of the name ‘-eyata- in Reyataz, especially if the dot in the letter “i” is left off or lacks prominence or if the letter “t” is not crossed.

Reyataz 300mg po qd
Rasilez 300mg po qd

The two names also sound similar due to the shared letters ‘R’ and ‘z’. However, the middle portions of the names ‘-asile-’ and ‘-eyeta-’ may sound different. The letter ‘a’ in Rasilez is usually pronounced with a short letter ‘a’ whereas the letter ‘e-’ in Reyataz are pronounced as a long ‘a’ sound. Additionally, the syllable ‘-il-’ in Rasilez and the syllable ‘-ya-’ in Reyataz are both pronounced with emphasis and sound different. Finally, the last syllable of each name sounds distinctly different (-lez vs. -taz). However, the two products share an overlapping strength (150 mg), dose (300 mg) and frequency of administration (once daily) which increases the potential for confusion. The Reyataz 300 mg dose should also be taken with 100 mg ritonavir and a light meal, but these additional directions for use may not always be included on a prescription. Nor will these drugs always be filled simultaneously or perhaps even at the same pharmacy.

DMETS has concerns regarding the look-alike similarities between these products should a prescription be written with the directions “300 mg orally once daily as directed”. The two names look similar and the overlapping characteristics increase the potential for confusion. Thus, DMETS believes that the tradenames Reyataz and Rasilez should not co-exist in the marketplace.

Additionally, DMETS reviewed the labels and labeling from a safety perspective. DMETS has identified the following areas of improvement, which might minimize potential user error.

F

1 Page(s) Withheld

 Trade Secret / Confidential

Draft Labeling

 Deliberative Process

Appendix A. DMETS prescription study results for Rasilez

Outpatient	Verbal	Inpatient
Rasiler	Rezalid	Rasilez
Rasiler	Rezilis	Rasilez
Ranier	Rasoliz	Rasilet
Rasiler	Rezulez	Pasilez
Rasiler	Rezulez	Rasilez
Ranler	Rezelez	Rosilez
Ranlez	rezalez	Rasilez
Rasiler	Rezalez	Rasilez
Rasiler	Rezulez	Rasilez
Ranler	Resolez	Rosilez
Rasiler	Rezelas	Rasilez
Rasiler	Resoliz	Rasilez
RASILER		Rasilez
Ranier		Rasilez
Rasiler		Rasilez
Rasiler		Rosilez
Ranier		Rasilez
Rasiler		Rasilez
Rasiler		Rasilez
Rasiler		Rasilez
Ranler		Rasilez
		Rasilez
		Rasilez

Appendix B. DMETS prescription study results for Tekturna

Outpatient	Verbal	Inpatient
Tehturne	Tecturna	Tekturna
Tekturine	Tecturna	Tekturna
Tektrine	Ecturna	Tekturna
Tekturine	Tecturna	Tekturna
Tekturine	Tacturna	Tekturna
Tenturine	Techturna	Tekturna
Tehturne	Techturna	Tekturna
Tenturine	Tecturna	Tekturna
Tekturine	Tecturna	Tekturna
Tehtirine	Tecturnal	Tekturna
Tebturne	Techterna	Tekturna
Teleturine	Tecturna	Tekturna
Tekturine	Tecturna	Tekturna
Tekturine	tecturna	Tekturna
tehturine	Techterna	Tekturna
Teleturine		Tekturna
Teleturine		Tekturna
Tekturna		Tekturna
		Tekturna
		Tekturna

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/s/

Laura Pincock
8/17/2006 02:05:13 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
8/17/2006 02:08:29 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/17/2006 04:29:48 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/17/2006 04:37:24 PM
DRUG SAFETY OFFICE REVIEWER



NDA 21-985

Novartis Pharmaceuticals Corporation
Attention: Elizabeth McCartney
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. McCartney:

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

We also refer to your July 11, 2006 correspondence, containing a proposal for an amendment of NDA 21-985 for an additional drug product manufacturing site.

We have reviewed the referenced material and have the following comments in response to your questions.

1. Does FDA agree that the proposed data package as outlined by Novartis supports the registration of a second drug product manufacturing facility?

Agency response: No, your proposal provides insufficient data to adequately assess the quality of the drug product manufactured at the proposed new drug product manufacturing site. Release and at least stability data from batches of each strength should be provided. A comparison of the impurities (degradants) and multi-point dissolution profiles from batches manufactured at the current and at the proposed site should be provided; any differences should be discussed and justified. Changes in the equipment, SOP's, environmental conditions, and controls in the manufacturing process at the alternate site should be discussed.

2. Does FDA agree that the proposed timeline for submitting the additional CMC information to support the second manufacturing facility can be done without any impact on the current NDA action date of December 13, 2006?

Agency response: As the addition of an alternative drug product manufacturing site requires an evaluation of the facility, and since your proposal involves data submission within the last 3 months of the review clock time, the review clock will likely be extended by 3 months.

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

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

/s/

Norman Stockbridge
8/16/2006 07:57:06 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 31, 2006

TO: John David, Regulatory Project Manager
Thomas Marciniak, MD, Medical Reviewer
Division of Cardiovascular and Renal Products

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dan-My T. Chu, PhD
Regulatory Review Officer
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-985

NME: Yes

APPLICANT: Novartis Pharmaceuticals

DRUG: Rasilez® (aliskiren)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of hypertension alone or in combination with other antihypertensive agents.

CONSULTATION REQUEST DATE: 4/5/06

DIVISION ACTION GOAL DATE: 9/1/06

PDUFA DATE: 12/13/06

I. BACKGROUND:

Novartis Pharmaceuticals Corporation submitted a New Drug Application 21-985 for Rasilez® (aliskiren) for the treatment of hypertension alone and in combination with other antihypertensive agents. Aliskiren is a new molecular entity and its proposed mechanism of action is inhibition of the first step of the renin angiotensin system (RAS). The RAS plays an important role in the regulation of blood pressure and volume homeostasis. Inhibitors of RAS such as aliskiren, which block the RAS at its first and rate-limiting step would serve as a more potent mechanism to control hypertension as it would inhibit the formation of both angiotensin I and

angiotensin II. Oral and intravenous administration of aliskiren to animals resulted in complete inhibition of plasma renin activity, sustained reductions in mean arterial pressure, and significant increases in plasma concentrations of active and total renin.

In support of the use of aliskiren for treatment of hypertension in humans, the sponsor conducted 5 placebo-controlled trials and 2 active-controlled trials. The results showed that aliskiren given once daily was both safe and efficacious in the treatment of hypertension.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State*	Protocol #	Insp. Date	EIR Received Date	Final Classification
2201-507 2308-542 2302-512 Robert S. Lipetz, DO	Spring Valley, CA	2201 2308 2302	5/22/06- 6/8/06	6/29/06	VAI
2201-541 Bronell E. Chandler, M.D.	Upper Darby, PA	2201	6/6/06- 6/12/06	7/11/06	VAI
2201-539 2203-512 2305-517 Edward T. Zawada Jr., M.D.	Sioux Falls, SD	2201 2203 2305	5/8/06- 5/11/06	6/15/06	NAI

*If international site, please insert column for country.

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

- A. **Protocol No: SPP100A 2201:** This study was a phase II multicenter, randomized, double-blind, placebo-controlled, parallel-group study with the primary objective of examining the blood pressure lowering effects of aliskiren (150, 300 or 600 mg) to placebo in patients with mild-to-moderate essential hypertension. The primary efficacy endpoint was the change from baseline (Visit 2) in mean sitting diastolic blood pressure (MSDBP) at trough measured by a calibrated standard sphygmomanometer. After written consent was obtained, subjects were examined for eligibility into the study. Patients currently taking antihypertensive medication were entered into a two week washout phase. At the end of the two week washout period (visit 1), subjects were again examined for eligibility and those that remained eligible entered the single-blind, placebo, run-in phase. Patients who were newly diagnosed with mild-to-moderate essential hypertension and who were not taking any antihypertensive medication(s), were directly enrolled into the single blind, placebo, run-in-period. At the end of the placebo, run-in phase (visit 2), eligibility of subjects was again confirmed and those who remained eligible were randomized equally in a double-blind fashion to either aliskiren (150, 300 or 600 mg), irbesartan (150 mg), or placebo once daily for 8-weeks. During the 8 week period, subjects were monitored bi-weekly for blood pressures. If at any visit, the MSDBP < 110 mm Hg and mean sitting systolic blood pressure (MSSBP) < 180 mm Hg, the patient was discontinued from the study. At the end of the 8 week period (visit 6), blood pressures were examined again. Four days after the last dose of study medication, the effect of drug withdrawal was evaluated by recording blood pressure and adverse events. In addition, at selected centers, additional blood pressure measurements will be obtained at Visit 4 and Visit 6 prior to dosing and again at 2, 4, and 6 hours after dosing for the assessment of trough-to-peak antihypertensive effect.

Inspected:

1. Robert S. Lipetz, D.O. 21 subjects
Encompass Clinical Research
10225 Austin Drive, Suite 203
Spring Valley, CA 91978
 - a. At this site, 37 subjects were screened, 21 subjects were randomized, 2 subjects withdrew or were discontinued from the study, and 19 subjects completed the study. An audit of 13 of 21 randomized subjects was conducted at this site.
 - b. There were no limitations to this inspection.
 - c. There were no significant deviations noted at this site.
 - d. Assessment of data integrity: The data generated as this site appear acceptable in support of the respective indication.

2. Bronell E. Chandler, M.D. 30 subjects
Mercy Wellness Center
6800 Market Street
Upper Darby, PA 19082
 - a. At this site, 51 subjects were screened, 30 subjects were randomized, 2 subjects withdrew or were discontinued, and 28 subjects completed the study. There was 1 SAE reported. Note that while 51 subjects were screened, the site had re-enrolled 6 subjects. These subjects were early terminated during the single-blind, placebo run-in phase due to problems with the site inadvertently being sent both randomized drug and placebo during this phase and subjects inadvertently given the randomized drug. The sponsor had granted approval to re-enroll these subjects after a 30 day washout period.
 - b. There were no limitations to this inspection.
 - c. The following were deviations noted at this site:
 - i. The investigator did not follow the investigational plan [21 CFR 312.60]. Specifically, subject #22 was initially terminated from the study and subsequently re-enrolled into the study at a later time without the sponsor's permission.
 - ii. The investigator did not maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)]. Specifically, the investigator incorrectly entered the data for blood pressure measurements from the source documents into the eCRF for 6 subjects:

Subject Number	Treatment Group	Visit Number / Date	True Source Data	Incorrectly Reported Data in Line Listing
26	Aliskiren 300 mg	V2 / 7-2-2003	3 rd DBP = ✓	3 rd DBP = ✓
18	Placebo	V2 / 6-4-2003	1 st SBP = ✓	1 st SBP = ✓
42	Placebo	V5 / 10-3-2003	2 nd DBP = ✓	2 nd DBP = ✓
39	Aliskiren 300 mg	V5 / 10-10-2003	2 nd SBP = ✓	2 nd SBP = ✓
34	Aliskiren 150 mg	V5 / 8-14-2003	3 rd DBP = —	3 rd DBP = —
45	Irbesartan 150 mg	V1 / 8-7-2003	2 nd SBP = —	2 nd SBP = —

iii. The investigator failed to report to the IRB an unanticipated problem resulting in risks to subjects [21 CFR 312.66]. Specifically, there was a drug mix-up where 8 subjects were inadvertently given randomized drug during the time in which the subjects were in the single-blind placebo run-in phase. This problem was due to the site being sent the both randomized drug and placebo during the placebo run-in phase. It was noted that as of the FDA audit, the site still had not reported this unanticipated problem to their IRB.

d. Assessment of data integrity: The majority of the data generated by this site may be used in support of the respective indication. However, DSI recommends that the review team consider the finding above where there were discrepancies noted in reporting of blood pressure (BP) measurements from the source document to the eCRF. The primary efficacy endpoint was the change from baseline (visit 2) in mean sitting diastolic blood pressure (MSDBP) at trough measured by a calibrated standard sphygmomanometer. Incorrect data entries of BP values made by the site into the eCRF would result in the sponsor having incorrect BP values and subsequently the sponsor incorrectly reporting these data to the FDA. We recommend that the review division evaluate the discrepancies in the BP values noted above to determine whether they impact the statistical significance of the data from this site in support of the NDA.

3. Edward T. Zawada Jr., M.D.
 North Central Kidney Institute
 911 E. 20th Street, Suite 601
 Sioux Falls, SD 57105

11 subjects

- a. At this site, 26 subjects were consented and screened, 11 subjects were randomized, 2 subjects discontinued from the study, and 9 subjects completed the study. No SAE's were reported for this site for this study. An audit of all 11 randomized subject records was conducted at this site.
 - b. There were no limitations to this inspection.
 - c. There were no significant deviations reported at this site.
 - d. Assessment of data integrity: The data generated at this site appear acceptable in support of the respective indication.
- B. Protocol No: SPP100A 2203:** This study was a phase IIb randomized, double-blind, placebo-controlled, multifactorial, multi-center, parallel group study with the primary objective (based on amendment 1) to confirm the blood pressure lowering effects of aliskiren (75, 150 or 300 mg) given alone versus placebo administered for 8 weeks to patients with uncomplicated diastolic essential hypertension (MSDBP > 95 mm HG and < 110 mmHG). The primary efficacy endpoint was the change from baseline to endpoint mean sitting diastolic blood pressure (MSDBP) at trough. After written consent was obtained, subjects were examined for eligibility into the study. Subjects currently taking antihypertensive medications were entered into a tapering phase where medications were discontinued. A prescreening visit was conducted on these subjects to determine eligibility to enter the 3 week single-blind placebo run-in period. All others not taking antihypertensive medication and who were eligible at visit 1, were directly entered into the 3 week single-blind placebo run-in period. At visit 2, patients were examined again for eligibility and those who did not meet the blood pressure eligibility criteria were allowed one additional week of placebo single-blind run-in in order to establish blood pressure eligibility. After evaluating eligibility again at visit 3 those who remained eligible were randomized to 1 of 11 treatment arms: aliskiren (75, 150 or 300 mg OD); valsartan (80, 160 or 320 mg OD); the combination of aliskiren and valsartan (75/80 mg, 150/160 mg, or 300/320 mg OD); valsartan and HCTZ 160/12.5 mg OD; or placebo OD. The first week post randomization was a forced titration period for patients randomized to aliskiren and valsartan 300/320 mg OD (i.e. Patients in this treatment group received aliskiren and valsartan 150/160 mg OD for one week, and were then titrated up.) Patients randomized to the other groups received their respective assigned doses through the 8 week period. Note that the original protocol stated that the treatment period was 6 weeks where amendment 1 of the protocol changed the treatment period to 8 weeks. For safety purposes, if at any visit, a patient gets severe hypertension (MSDBP \geq 110 mmHg or MSSBP \geq 180 mmHg) or presents with signs or symptoms of hypotension (MSDBP < 60 mmHg and/or a MSSBP < 100 mmHg), the patient was permanently discontinued from the study.

Inspected:

Edward T. Zawada Jr., M.D.
North Central Kidney Institute
911 E. 20th Street, Suite 601
Sioux Falls, SD 57105

16 subjects

- a. At this site, 39 subjects were consented and screened, 16 subjects were randomized, 4 subjects discontinued from the study, and 12 subjects completed the study. No SAE's were reported for this site for this study. An audit of 12 of 16 randomized subject records was conducted at this site.
- b. There were no limitations to this inspection.
- c. There were no significant deviations reported at this site.

- d. Assessment of data integrity: The data generated by this site appear acceptable in support of the respective indication.

C. **Protocol No: SPP100A 2302:** This study was a phase III randomized, open-label, multicenter, parallel-group, dose escalation study with the primary objective of assessing the long-term safety and tolerability of aliskiren 150 mg and aliskiren 300 mg, with the optional addition of hydrochlorothiazide (HCTZ) 12.5 mg or 25 mg to aliskiren 300 mg, in patients with uncomplicated essential hypertension (mean sitting diastolic blood pressure (MSDBP) \geq 90 mmHg and $<$ 110 mmHg). The primary efficacy endpoint is the change in MSDBP from baseline. After written informed consent has been obtained, eligibility will be determined at Visit 1. Subjects currently on anti-hypertensive medication were tapered off within one-week. At Visit 2, eligibility was examined again and those that remained eligible entered the 2-4 week drug free screening period. Patients with newly diagnosed uncomplicated hypertension currently not taking any drugs or subjects who have stopped taking antihypertensive drugs for at least 1 week were directly enrolled into the 2-4 week drug free screening period (i.e. Visits 1 and 2 are combined). At the end of the drug free screening period (visit 3), eligibility was examined again and those that remained eligible were randomized in a 3:2 ratio to aliskiren 150 or 300 mg once daily. At visits 5 and 6 (end of treatment month 2 and 3) investigators titrated individual therapy for their study patients in order to achieve a goal BP of $<$ 140/90 mmHg. At these visits, patients receiving aliskiren 150 mg were increased to 300 mg, patients receiving aliskiren 300 mg had 12.5 mg of HCTZ added, and patients receiving aliskiren 3000 mg with HCTZ 12.5 mg had an increased dose of HCTZ to 25 mg. At visit 7 (end of treatment month 4) and thereafter, up-titration to the next treatment step only occurred if the patient's BP was persistently (2 consecutive visits) \geq 140/90 mmHg. Down titration of aliskiren was not permitted during the study; however, down titration or discontinuation of HCTZ was permitted, at the discretion of the investigator. Open-label, active treatment will continue for a minimum of 52 weeks. For safety purposes, patients with severe hypertension (MSDBP \geq 110 mmHg or MSSBP \geq 180 mmHg) or patients with signs or symptoms of hypotension (MSDBP $<$ 60 mmHg and/or a MSSBP $<$ 100 mmHg) were permanently discontinued from the study.

Inspected:

Robert S. Lipetz, D.O.
Encompass Clinical Research
10225 Austin Drive, Suite 203
Spring Valley, CA 91978

7 subjects

- a. At this site, 12 subjects were screened, 7 subjects were randomized, and 4 subjects completed the study.
- b. There were no limitations to this inspection.
- c. There were no significant deviations at this site.
- d. Assessment of data integrity: The data generated as this site appear acceptable in support of the respective indication.
- D. **Protocol No: SPP100A 2305:** This was a phase III double-blind, randomized, multicenter, parallel group study with the primary objective of evaluating the efficacy of the combination of aliskiren 150 mg and amlodipine 5 mg in patients with essential hypertension not fully responsive to amlodipine 5 mg. The primary efficacy endpoint was the change from baseline (Visit 4, Day 1) to endpoint (Visit 7, Day 42) in mean sitting diastolic blood pressure (MSDBP) at trough, as measured by the automatic blood pressure monitor and appropriate size cuff. After written informed consent was obtained, all patients underwent a two week washout period. During this time, patients currently on antihypertensive medications were tapered off per investigator instruction and manufacturer's labeling. At Visit 2,

eligibility was examined again and those that remained eligible entered the single blind treatment phase with amlodipine 5 mg once daily for four weeks. At Visit 4 (Day 1) patients not adequately responsive to amlodipine 5 mg (MSDBP \geq 90 mmHg) and who remained eligible were equally randomized to receive amlodipine (5 or 10 mg), or the combination of aliskiren 150 mg and amlodipine 5 mg for 6 weeks. Those that responded to amlodipine 5 mg (MSDBP $<$ 90 mmHg) at Visit 4 were discontinued from the study. At the end of the 6 weeks (Visit 7) or upon early termination, blood pressure and other measurements were taken. For safety purposes, if at any time during the study patients developed severe hypertension (MSDBP \geq 110 mmHg or MSSBP \geq 180 mmHg), they were permanently discontinued from the study or if patients developed signs or symptoms of hypotension (MSDBP $<$ 60 mmHg and/or a MSSBP $<$ 100 mmHg), they were to be evaluated by the investigator and if clinically warranted, be permanently discontinued from the study.

Inspected:

Edward T. Zawada Jr., M.D.
North Central Kidney Institute
911 E. 20th Street, Suite 601
Sioux Falls, SD 57105

2 subjects

- a. At this site, 24 subjects were consented and screened, 2 subjects were randomized and 2 subjects completed the study. No SAE's were reported for this site for this study. An audit of 2 randomized subject records was conducted.
 - b. There were no limitations to this inspection.
 - c. There were no significant deviations reported at this site.
 - d. Assessment of data integrity: The data generated by this site appear acceptable in support of the respective indication.
- E. **Protocol No: SPP100A 2308:** This study was a phase III randomized, double-blind, placebo-controlled, parallel-group, multicenter study with the primary objective of evaluating the blood pressure effects of aliskiren (150, 300 or 600 mg) to placebo in patients with essential hypertension. The primary efficacy endpoint was the change from baseline MSDBP to trough. After written informed consent was obtained, eligible patients were tapered off their current antihypertensive medication. All patients were to be completely off previous antihypertensive medication for at least one week prior to entering the single-blind period. Patients newly diagnosed with uncomplicated hypertension and who were not taking any antihypertensive medication(s), or patients that had not been taking antihypertensive drugs for 1 week prior to Visit 1, could combine Visits 1 and 2 and be enrolled directly into the two to four week single-blind run-in period. At Visit 2 patients entered the single-blind placebo run-in period and received placebo for 2 weeks. After 2 weeks, eligibility of patients for randomization was determined. Patients who did not meet the blood pressure eligibility criteria after 2 weeks of the single-blind run-in period were allowed 2 additional weeks of placebo single-blind run-in. At Visit 3, eligible subjects were randomized in a double-blind fashion to one of four treatment groups: aliskiren (150 mg, 300 mg, or 600 mg) or placebo OD. All patients were to return to the study center every 2 weeks during the 8-week double-blind treatment period. At Visit 7, patients returned to the study center and were instructed to stop taking their double-blind study medication. Patients then entered a 2-week drug withdrawal period. For safety purposes, if at any time during the study, patients developed severe hypertension (MSDBP \geq 110 mmHg or MSSBP \geq 180 mmHg) then they were to be permanently discontinued from the study. If however, patients had signs or symptoms of hypotension (MSDBP $<$ 60 mmHg and/or a MSSBP $<$ 100 mmHg), they were to be evaluated by investigator and if clinically warranted, be permanently discontinued from the study.

Inspected:

Robert S. Lipetz, D.O.
Encompass Clinical Research
10225 Austin Drive, Suite 203
Spring Valley, CA 91978

10 subjects

- a. At this site, 11 subjects were screened, 10 subjects were randomized, and 9 completed the study. An audit of 10 subject records was conducted at this site.
- b. There were no limitations to this inspection.
- c. The following deviation was noted at this site: The investigation found that the investigator did not follow the investigational plan [21 CFR 312.60]. Specifically, protocol SPP100A 2308 specified that subjects were not to take the final dose of medication at visit 7. We noted that 8 subjects (#00001, #00003, #00004, #00005, #00006, #00007, #00008, #00010) were given the last dose of study medication at visit 7.
- d. Assessment of data integrity: The data generated at this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

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.

{See appended electronic signature page}

Dan-My T. Chu, PhD
Regulatory Review Officer

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dan-My Chu
8/14/2006 02:16:31 PM
UNKNOWN

Leslie Ball
8/16/2006 06:24:19 PM
MEDICAL OFFICER

G

b

_____ Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process



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 Rasilez (aliskeren) 150 mg and 300 mg tablets.

We also refer to your July 6, 2006 submission, containing answers to questions from the "Response to Health Authority Questions" dated June 29, 2006.

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

Comment on Response #1: The pre-NDA meeting minutes only address unambiguously that narratives did not have to be submitted for discontinuations. Whether any agreements extended to CRFs for discontinuations is not clear from our minutes. Regardless, after having seen the NDA submission, we believe that CRFs for many discontinuations will be needed for a complete review of the submission. We will request additional CRFs to be submitted as further review suggests and as agreed upon at the pre-NDA meeting. We will not insist at this time that all CRFs for discontinuations be submitted provided that requested CRFs are provided promptly (see next Comment).

Comment on Response #2: We have not requested "detailed clinical documentation." We are requesting the CRFs (the "all other available clinical documentation" are the other documents that we consider part of the CRFs as we discussed at the pre-NDA meeting), August 15 is not an acceptable response time for complying with this request. For additional CRFs requested, we expect a turnaround time of one week or less. If you are unable to meet such a turnaround, we will insist that you provide CRFs for all discontinuations immediately and we will compile as rapidly as possible a list of any other CRFs that we may possibly need for a complete review. The 120 data safety update does not address our concerns.

Comment on Response #3: Providing the results of Study 2327 in October or November 2006 will not allow time for a thorough review.

We believe that it is in your best interest to compile and submit the results from Study 2327 as rapidly as possible.

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
7/25/2006 02:34:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-985

Novartis Pharmaceuticals Corporation
Attention: Kimberly Dickerson, Pharm.D.
One Health Plaza
East Hanover, New Jersey 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 Rasilez (aliskiren) 150 mg and 300 mg Tablets.

We also refer to your submissions dated March 13, 14, 17 and 31 and April 3, 4 and 5, 2006.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 14, 2006 in accordance with 21 CFR 314.101(a).

If you have any questions, please call:

Mr. John David
Regulatory Project Manager
(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
4/24/2006 10:57:49 AM

REQUEST FOR CONSULTATION

TO (Office/Division): **Bai Nguyen OPS/PARS**

FROM (Name, Office/Division, and Phone Number of Requestor): **Scott N. Goldie, Ph.D.**

**Regulatory Health Project Manager
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research**

DATE
06-APR-2006

IND NO.

NDA NO.
21-985

TYPE OF DOCUMENT
N 000

DATE OF DOCUMENT
10-FEB-2006

NAME OF DRUG
Rasilez Tablets

PRIORITY CONSIDERATION
S

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
July 2006

NAME OF FIRM: **Novartis**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

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

**COMMENTS / SPECIAL INSTRUCTIONS: Environmental Assessment (EA) Consult.
EIC exceeds 1 ppb. NDA 21-985 is in EDR (EA section provided electronically)**

SIGNATURE OF REQUESTOR
Scott Goldie.

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Xavier Ysern
4/6/2006 01:49:03 PM
signing for Scott Goldie

DSI CONSULT: Request for Clinical Inspections

Date: 4/5/06

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Leslie K. Ball, M.D., Branch Chief, GCP2, HFD-47

Through: Joseph Salewski, Acting Director
Division of Scientific Investigations, HFD-45

From: John David, Regulatory Health Project Manager
Division of Cardiovascular & Renal Products, HFD-110

Subject: **Request for Clinical Site Inspections**
Application: NDA 21-985
Sponsor: Novartis Pharmaceuticals Corporation
Drug: Rasilez (aliskiren) Tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: hypertension
This drug is a New Molecular Entity (NME)

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
2201-507 2308-542 2302-512 Robert S. Lipetz, D.O. Encompass Clinical Research 10225 Austin Drive, Suite 203 Spring Valley, CA 91978 619-660-9068	2201 2308 2312 (long term f/u)	21 10 7	hypertension
2201-541 Bronell E. Chandler, M.D. Mercy Wellness Center 6800 Market Street Upper Darby, PA 19082 610-734-7434	2201	30	hypertension

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
2201-539 2203-512 2305-517 Edward T. Zawada Jr., M.D. North Central Kidney Institute 911 E. 20 th Street, Suite 601 Sioux Falls, SD 57105 605-322-5800	2201 2203 2305	11 16 2	hypertension

Domestic Inspections:

We have requested inspections because (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): high placebo effect

International Inspections:

We have requested inspections because (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify):

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by 9/1/06. We intend to issue an action letter on this application by 12/13/06. The PDUFA due date for this application is 12/13/06.

Should you require any additional information, please contact *John David, RHPM* at Ph: 301-796-1059

Concurrence: (as needed)

Thomas Marciniak, M.D., Medical Team Leader/Medical Reviewer

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/s/

John David

4/5/2006 03:37:56 PM

H

8 Page(s) Withheld

 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): Mail: Corine Kulick, OMP/DDMAC, WO22, RM1450, 10903 New Hampshire			FROM: LCDR John David, RHPM, HFD-110		
DATE 3/3/06	IND NO. 62,976	NDA NO. 21-985	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT 3/3/06	
NAME OF DRUG Rasilez (aliskiren)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Renin Inhibitor	DESIRED COMPLETION DATE 5/3/06	
NAME OF FIRM: Novartis Pharmaceuticals Corp.					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): electronic NDA	
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the labeling 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. Thank you!					
SIGNATURE OF REQUESTER John David			METHOD OF DELIVERY (Check one) X MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

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/s/

John David
3/2/2006 11:12:29 AM

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**PRESCRIPTION DRUG USER FEE
COVERSHEET**

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

1. APPLICANT'S NAME AND ADDRESS

NOVARTIS PHARMACEUTICALS CORP
Angie Young
One Health Plaza
East Hanover NJ 07936
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-985

2. TELEPHONE NUMBER

862-778-8685

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

Rasilez (aliskiren)

6. USER FEE I.D. NUMBER

PD3006425

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

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

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

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

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

Angie Young

TITLE

Director

DATE

2/6/06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$767,400.00

Form FDA 3397 (12/03)

(IBE PRMT CLOSE G) (Print Cover sheet)

REQUEST FOR CONSULTATION

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

FROM: Dr. Norman Stockbridge
Acting Division Director
Division of Cardiovascular and Renal Products

DATE
December 5, 2005

IND NO.
62,976

NDA NO.
N/A

TYPE OF DOCUMENT
General Correspondence
Serial 169

DATE OF DOCUMENT
November 22, 2005

NAME OF DRUG
aliskiren

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
renin inhibitor

DESIRED COMPLETION DATE
February 6, 2006

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

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

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
 BIOAVAILABILITY 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: 1st choice RASILEZ; 2nd choice TEKTURNA (Indication: hypertension)
Hard copy of the submission will be forwarded to Diane Smith, Project Manager. Novartis plans on submitting their NDA in February-March 2006. They would like our comments as soon as possible.

PDUFA DATE: N/A
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
Daryl Allis, Project Manager 301-796-1034

METHOD OF DELIVERY (Check one)
 DFS ONLY MAIL HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Daryl L. Allis
12/5/2005 10:00:28 AM

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3 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Food and Drug Administration



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: 973-781-3590

Attention: Dr. Kimberly Dickerson

Company Name: Novartis Pharmaceuticals Corporation

Phone: 862-778-4576

Subject: Meeting Minutes

Date: September 6, 2005

Pages including this sheet: 5

From: Daryl Allis
Phone: 301-594-5332
Fax: 301-594-5495
Email: allisd@cder.fda.gov

You are responsible for notifying us of any significant differences in understanding that you may have regarding the meeting outcomes (as reflected in the minutes).

Please let me know when you receive this. Thank you.

Minutes of a Meeting

Date of Meeting: August 29, 2005 (Sponsor's request)
IND Application: 62,976
Drug: Aliskiren (SPP-100) Tablets
Sponsor: Novartis Pharmaceuticals Corporation

Request Date: July 18, 2005
Sponsor Notified: July 20, 2005 (telephone)
Confirmation Date: July 20, 2005 (fax)
Package Received: August 15, 2005

Meeting Type: A
Classification: Clinical Pharmacology/ Biopharmacology: Dissolution/Bioequivalence
Purpose: Discuss the request for a waiver from the conduct of a bioequivalence study to compare the non-encapsulated tablet and over encapsulated tablet

Meeting Chair: Norman Stockbridge, M.D., Ph.D.
Meeting Recorder: Daryl Allis

FDA Participants

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Medical Officer, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Shari Targum, M.D.	Acting Team Leader, Medical Officer, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacologist, HFD-860
Lydia Velazquez, Pharm.D.	Clinical Pharmacologist/Biopharmacist, HFD-860
Daryl Allis, R.N., M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Novartis Participants

Debbie Aleknavage	Associate Director, Liaison Office, Drug Regulatory Affairs
Vijay Bahagava, Ph.D.	Global Head & Vice President, DMPK
Adrian Birch	Vice President, Drug Regulatory Affairs
Kimberly Dickerson, Pharm.D.	Assistant Director, Drug Regulatory Affairs
Dan Howard, Ph.D.	Global Head, Pharmacokinetics, DMPK
Yatindra Joshi, Ph.D., M.B.A.	Vice President, Pharmaceutical and Analytical Development
Elizabeth McCartney	Group Head, US Liaison Activities, Regulatory CMC
Andrew Satlin, M.D.	Executive Director, Clinical Research & Development
Sujata Vaidyanathan, Ph.D.	Senior Lead Pharmacokineticist, Pharmacokinetics, ED-DMPK
Steven Zelenkofske, D.O.	Sr. Medical Director, US Clinical Development & Medical Affairs

Background

Novartis Pharmaceuticals Corporation is developing aliskiren (SPP 100), an oral formulation of a renin inhibitor, for the indication of safe and effective once-daily therapy for the treatment of hypertension, alone or in combination with other antihypertensive agents. Novartis requested this opportunity to present their scientific rationale that they believe support that their blinded clinical formulation is similar to their final

market image tablets. They are requesting a waiver for a bioequivalence study comparing the non-encapsulated tablet to the over-encapsulated tablet used for blinding in the clinical studies.

Early studies in healthy volunteers and in patients conducted under IND 62,976 were done by Speedel Pharmaceuticals of Bridgewater, NJ. The ownership of the IND was transferred to Novartis Pharmaceuticals Corporation effective September 1, 2002. Previous meetings and correspondence between the Division and the Sponsor discussing this issue include:

- EOP 2 CMC meeting on September 22, 2004
- Pre-NDA meeting on April 20, 2005
- Telephone conversation with Drs. Marroum and Velazquez on June 20, 2005

Topics for Discussion

General

Novartis presented a summary of data to support their argument to demonstrate that the loose fillers added to the capsules for blinding did not change the integrity of the tablet. They submitted dissolution data in various media, clinical data from two separate studies between the over-encapsulated and non-encapsulated formulations, and finally permeability data. The fillers were added to prevent the tablet from moving inside the capsule. They stated that (1) the capsule disintegrated within 2 to 5-minutes, (2) the tablet integrity and composition for the two formulations did not change, (3) the tablet was completely dissolved in 30-minutes, (4) the PK profiles were similar between the over-encapsulated and non-encapsulated formulations, and (5) the time to peak plasma levels is much longer than the dissolution time, so dissolution is not rate-limiting. In addition, they believe the tablets would behave in solution in the same manner for both the over-encapsulated and non-encapsulated formulations. Therefore, they are requesting a waiver for conducting a bioequivalence (BE) study comparing these two formulations.

The Division agreed that the dissolution profiles looked similar. Dr. Stockbridge asked if they have data from other trials that show the plasma dose-response curves look similar for the over-capsulated and non-capsulated formulations. Novartis stated that they would have data from recently completed studies that show an effect on blood pressure, but they would not have PK data from these studies.

The Division noted that there was a wide variability in C_{max} for the non-encapsulated tablet. In addition, we explained that we have recent experience with a drug product that had a large inter- and intra-subject variability which resulted in major review issues. We asked if they had inter- and intra-subject variability data for these two formulations. They stated the intra-subject variability was 20% to 40% for the tablets only, and they have PK data for the same subject on multiple occasions. In addition, the PK data are linear for doses studied from 75 to 600-mg. However, they do not have intra-subject variability data with the over-encapsulated formulation. The high variability reported in previous meeting minutes referred to inter-subject variability.

Dr. Velazquez stated that the request for the waiver for the BE study was thoroughly reviewed and discussed within the Division of Pharmaceutical Evaluation I. Their decision was that a BE study would be required because the magnitude of change in the weight of the fillers used for the over-encapsulated tablets was in excess for a SUPAC Level 3 Change, specifically an increase for the 75-mg and 150-mg tablets, respectively. The reference article (Bhagwant D. Rege, et al, 2001) provided in the briefing package that discussed biowaivers for low permeability drugs, to date, has not been accepted by the Agency; we have always followed the SUPAC IR guidance in situations like these.

Dr. Stockbridge thought there was a pretty good argument that the similarly fast dissolution should result in very similar bioequivalence, but he was concerned that the cross-study comparison of Cmax showed as great a difference as it did.

When the drug product permeability was discussed, Dr. Velazquez stated that she believed the drug had a low permeability. Novartis believes the drug has low permeability at low doses, but the permeability increases at higher concentrations.

The design of the recommended BE study was discussed. The Division inquired about the dose-response curve; Novartis stated that aliskiren had a shallow dose-response. They were concerned that considering the variability, a BE study would require up to 125 subjects. Dr. Stockbridge stated that if this trial is sized appropriately and the confidence limits are narrow around the drug effect at the 75- and 150-mg doses, he did not think that they would need necessarily to meet the 80 to 125 range.

Conclusions/Recommendations

- Novartis agreed to conduct a BE study comparing the over-encapsulated and non-encapsulated formulations of the drug products in healthy normal volunteers.
- The Division agreed to review and provide timely comments on the proposed study protocol that would focus on the 150-mg dose.
- Novartis plans on submitting the NDA for aliskiren for the treatment of hypertension in mid-February 2006. They would provide a preliminary report for the BE study in the NDA submission.
- The Division agreed to accept the final study report for the BE study within the first 4-months of the NDA review cycle. It is likely that this NDA would receive a standard 10-month review.

Meeting Recorder: *{See appended electronic signature page}*
Daryl Allis, R.N., M.S., F.N.P.

Concurrence Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Draft	08/30/05	Final	09/06/05
RD:			
Velazquez	08/30/05		
Marroum	08/30/05		
Targum	08/30/05		
Marciniak	08/30/05		
Karkowsky	08/30/05		
Stockbridge	08/31/05		

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/s/

Daryl L. Allis

9/6/2005 02:06:20 PM

A copy of the minutes will be faxed to
the sponsor following Dr. Stockbridge's signature.

Norman Stockbridge

9/7/2005 08:30:16 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

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

Dear Dr. Dickerson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aliskiren (SPP-100) Tablets.

We also refer to your amendment dated May 2, 2005 (serial # 112), containing a protocol amendment for Study No. 2302 to include a one month, double-blind, placebo-controlled, randomized drug withdrawal period in a subset of patients after 11-months of open-label treatment.

We have completed the medical review of your submission and have the following comments and recommendations.

The randomized withdrawal should add valuable information regarding long-term efficacy of aliskiren. The detection of a rebound effect is limited by the first return visit post-withdrawal at 1 week.

We recommend a BP check at 2-3 days post-withdrawal for documenting that there are no rebound effects from aliskiren withdrawal. In addition, we recommend that you consider alternative timings for checking for rebound, e.g., a sparse sampling approach for checking for rebound with the day of the check varying for different patients may be useful because the timing of rebound (if any) is not known.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
6/27/05 06:49:36 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

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

Dear Dr. Dickerson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aliskiren (SPP-100) Tablets.

We also refer to your amendment dated April 21, 2005 (serial # 108), containing a toxicology report entitled "Expert statement and toxicological assessment of _____ Aliskiren drug substance intermediate."

We have completed the review of your submission, and we agree that the negative Ames test alone constitutes sufficient evidence that the _____ in question _____ is not a mutagen. However, it should be noted that the full study report has not been made available to the Division. Our standing on this issue might change if we arrive at a different conclusion after our review of the full study report.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

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

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/s/

Norman Stockbridge
6/20/05 10:19:05 AM

Memo to the File

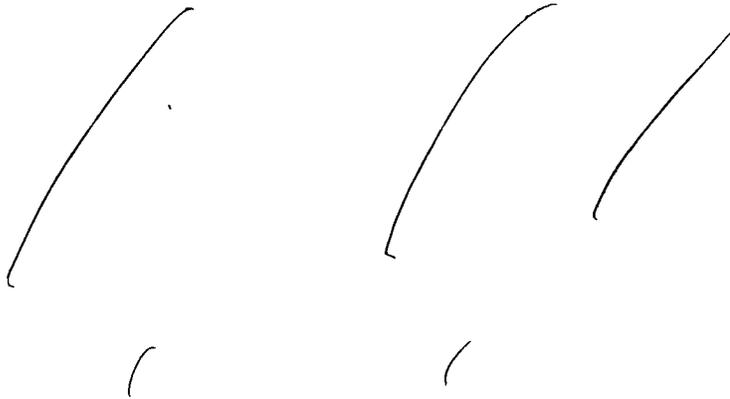
Date: May 26, 2005
From: Daryl Allis, RN, MS, FNP
Regulatory Health Project Manager, HFD-110
To: IND 62,976 Aliskiren
Subject: Pre-NDA meeting minutes clarification

Novartis Pharmaceuticals Corporation is developing Aliskiren, an oral renin inhibitor, for the treatment of hypertension. A Pre-NDA meeting was held between Novartis and the Division of Cardio-Renal Drug Products on April 20, 2005. Novartis requested (serial # 116) clarification regarding the following issues noted in the Division's meeting minutes.

1. The second bullet point on page 4 of the minutes refers to the submission of raw data for all studies. This issue was agreed to for all relevant studies conducted by Novartis; it does not include very early studies performed by Speedel, the original holder of the IND, with variant formulations. Novartis would provide copies of relevant reports written by Speedel, but not the raw data. Their NDA would contain all requisite data generated by Novartis for the product they intend to market.

Dr. Marroum, Team Leader, Office of Clinical Pharmacology and Biopharmaceutics, agreed.

2. Page 6 of the minutes summarizes a situation concerning 



Concurrence of the clarification points noted above was conveyed to the sponsor in a telephone conversation between Mr. Adrian Birch, Executive Director, Drug Regulatory Affairs, Novartis and Daryl Allis, Project Manager, Division of Cardio-Renal Drug Products on May 24, 2005.

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/s/

Daryl L. Allis
5/26/05 11:22:24 AM
CSO

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: 973-781-3590

Attention: Mr. Adrian Birch

Company Name: Novartis Pharmaceuticals Corporation

Phone: 862-778-3589

Subject: Meeting Minutes

Date: April 26, 2005

Pages including this sheet: 8

From: Daryl Allis
Phone: 301-594-5332
Fax: 301-594-5495
Email: allisd@cderr.fda.gov

You are responsible for notifying us of any significant differences in understanding that you may have regarding the meeting outcomes (as reflected in the minutes).

Please let me know when you receive this. Thank you.

Minutes of a Teleconference

Date of Meeting: April 20, 2005
IND Application: 62,976
Drug: Aliskiren (SPP-100) Tablets
Sponsor: Novartis Pharmaceuticals Corporation

Request Date: March 21, 2005
Sponsor Notified: March 23, 2005 (telephone)
Confirmation Date: March 28, 2005 (fax)
Package Received: April 5, 2005

Meeting Type: B
Classification: Pre-NDA
Purpose: Discuss formatting issues related to submitting the NDA for aliskiren for the treatment of hypertension, and gain the Division's concurrence with Novartis' proposed strategy for pooling efficacy and safety data.

Meeting Chair: Thomas Marciniak, M.D.
Meeting Recorder: Daryl Allis

FDA Participants

Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Lydia Velazquez, Pharm.D.	Clinical Pharmacologist/Biopharmaceutist, HFD-860
Sharon Gershon, Pharm.D.	Reviewer, Division of Scientific Investigations, HFD-46
Daryl Allis, R.N., M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Novartis Participants

Adrian Birch	Executive Director, Drug Regulatory Affairs
Yann Tong Chiang, Ph.D.	Director, Biostatistics
Kimberly Dickerson, Pharm.D.	Assistant Director, Drug Regulatory Affairs
Catherine Ford	Associate Director, Global Regulatory CMC
Marjorie Gatlin, M.D.	Executive Director, Clinical Development & Medical Affairs
Leonard Gonasun	Senior Director, Clinical Research & Development
Deborah Keefe, M.D.	Senior Director, Clinical Research & Development
Sheryl Manfreda	Clinical Registration Leader, Clinical Research & Development
Andrew Satlin, M.D.	Executive Director, Clinical Research & Development
Leigh Strachan	Project Manager, Drug Regulatory Affairs Operations
Jin Zhu, Ph.D.	Associate Director, Biostatistics
Ian Nichols, B.Sc.	Registered Toxicologist, Preclinical Safety

Background

Novartis Pharmaceuticals Corporation is developing aliskiren (SPP 100), an oral formulation renin inhibitor, for the indication of safe and effective once daily therapy for the treatment of hypertension, alone or in combination with other antihypertensive agents. Aliskiren is potent and selective inhibitor of human renin, the enzyme responsible for the production of angiotensin I. The effects on the renin-angiotensin system (RAS) provide the pharmacologic rationale for renin inhibition in the treatment of

hypertension. Novartis requested this meeting to discuss formatting issues related to submitting the NDA, and gain the Division's concurrence with Novartis' proposed strategy for pooling efficacy and safety data.

Early studies in healthy volunteers and in patients conducted under IND 62,976 were done by Speedel Pharmaceuticals of Bridgewater, NJ. The ownership of the IND was transferred to Novartis Pharmaceuticals Corporation effective September 1, 2002. Previous meetings and correspondence between the Division and the Sponsor include:

- Pre-IND meeting, November 8, 2000
- Pre-IND CMC meeting November 9, 2000
- EOP 2 meeting on February 11, 2004
- Special Protocol Assessment: Clinical meeting on July 12, 2004
- EOP 2 CMC meeting on September 22, 2004

Questions

1. **Does the Division agree with our proposed pooling strategy for trial included in the SCE and SCS and the proposal for patient narratives?**

The Division agreed.

The Division requested that the case report forms be complete to include all data that were collected for serious adverse events (AEs) and include copies of the Medwatch form and other documents such as hospital discharge summaries (if they were obtained as part of the sponsor's evaluation of the AE). If a review determines that other AEs are of concern, the Division might request that you submit the case report form for review during the review period. Novartis agreed.

Novartis explained that they did not plan on submitting narrative reports for study drop-outs. The Division agreed that the proposed plan for reporting was acceptable. Dr. Marciniak stated that we would need reports for all serious AEs, deaths and other events as requested. Novartis agreed.

2. **Does the Division agree with our proposal NOT to pool results of the studies conducted by Speedel, the previous IND holder? Does the Division agree with the proposed information to be included for the Speedel studies?**

The Division agreed.

3. **Does the Division agree with our proposal to submit an integrated summary of laboratory data in International Units?**

The Division agreed with the request that the laboratory reference ranges be provided. Novartis agreed.

4. **Does the Division have any other comments on our proposals?**

Clinical Pharmacology/Biopharmaceutics

The Division requested and Novartis agreed to provide the following under section 6 with the NDA submission in addition to what they stated they would submit under section 6:

- In vitro CYP450 and GPg studies
- Metabolic characterization of aliskiren
- Assay validation and methodology study results for all studies that involved PK