- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug?

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Quynh Nguyen
5/16/2007 11:34:57 AM
CSO

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Lisa Hubbard, RPh, Regulatory Review Officer, Division of Drug Marketing, Advertising, and Communication (DDMAC)

FROM:
Quynh Nguyen, Project Manager
OND/Division of Cardiovascular and Renal Products (DCRP)
Ph: (301) 796-0510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5-7-07		22-107	NDA submission	March 19, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tekturna HCT (aliskiren/HCTZ) Tablets	Standard	Anti-hypertensive	November 1, 2007

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Novartis has submitted a new NDA for Tekturna HCT, a fixed combination of aliskiren/HCTZ tablets for the treatment of hypertension. Please review the proposed labeling (carton, container, PI, and PPI) for this new NDA. The submission is located in the EDR at: **\\CDSESUB1\NONECTD\N22107\N_000\2007-03-19** in the **labeling** folder. Please contact John David, RPM, if you have any questions. Thanks!

PDUFA goal date: January 20, 2008
Labeling meetings: Lisa, John David will invite you to the mid-cycle and labeling meetings once they are scheduled.

SIGNATURE OF REQUESTER Quynh Nguyen, RPM	METHOD OF DELIVERY (Check one) ☐ MAIL XX DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Quynh Nguyen
5/7/2007 11:22:58 AM

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Office of Surveillance and Epidemiology (OSE)
Attention: Tanya Clayton, RPM
Mary Dempsey, Project Management Officer

FROM:
Quynh Nguyen, Project Manager
OND/Division of Cardiovascular and Renal Products (DCRP)
Ph: (301) 796-0510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5-7-07		22-107	NDA submission	March 19, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tekturna HCT (aliskiren/HCTZ) Tablets	Standard	Anti-hypertensive	November 1, 2007

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
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- ☐ 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:

Novartis has submitted a new NDA for Tekturna HCT, a fixed combination of aliskiren/HCTZ tablets for the treatment of hypertension. Please review the proposed RMP for this new NDA. The RMP submission is located in the EDR at: **\\CDSESUB1\NONECTD\N22107\N_000\2007-03-19** in the **Other** folder. Please contact John David, RPM, if you have any questions. Thanks!

PDUFA goal date: January 20, 2008
Labeling meetings: Please let John David know who the OSE reviewers will be so they can be invited to the mid-cycle and labeling meetings once they are scheduled.

SIGNATURE OF REQUESTER Quynh Nguyen, RPM	METHOD OF DELIVERY (Check one) ☐ MAIL XX DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Quynh Nguyen
5/7/2007 11:18:03 AM

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

REQUEST FOR CONSULTATION

TO (Division/Office):
Office of Surveillance and Epidemiology (OSE)
Attention: Tanya Clayton, RPM

FROM:
Quynh Nguyen, Project Manager
OND/Division of Cardiovascular and Renal Products (DCRP)
Ph: (301) 796-0510

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
5-7-07		22-107	NDA submission	March 19, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tekturna HCT (aliskiren/HCTZ) Tablets	Standard	Anti-hypertensive	November 1, 2007

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
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- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- XX OTHER *(SPECIFY BELOW)*: Review and comment on proposed tradename and labeling

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

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- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
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V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Novartis has submitted a new NDA for Tekturna HCT, a fixed combination of aliskiren/HCTZ tablets for the treatment of hypertension. Please review the proposed tradename and labeling (carton, container, PI, and PPI) for this new NDA. (There is also an RMP, but I will send a separate consult request for the RMP per your instructions.) The submission is located in the EDR at: **\\CDSESUB1\NONECTD\N22107\N_000\2007-03-19** in the **labeling** folder. Please contact John David, RPM, if you have any questions. Thanks!

PDUFA goal date: January 20, 2008
Labeling meetings: Please let John David know who the OSE reviewers will be so they can be invited to the mid-cycle and labeling meetings once they are scheduled.

SIGNATURE OF REQUESTER Quynh Nguyen, RPM	METHOD OF DELIVERY (Check one) ☐ MAIL XX DFS
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Quynh Nguyen
5/7/2007 11:13:51 AM

NDA No. 22-107

SPH100

(aliskiren/hydrochlorothiazide)

Film-Coated Tablets

Field Copy Certification Statement 21 CFR 314.50(k)(3)

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

Name: Fernando Marcella Date: 09-Mar-2007

Signature

Title: Associate Director

Department: Global Regulatory CMC

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

pleted form must be signed and accompany each new drug or biologic product application and each new supplement. See tions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. nent 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	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NOVARTIS PHARMACEUTICALS CORP Lina Thomas One Health Plaza East Hanover NJ 07936 US	22-107
2. TELEPHONE NUMBER 862-778 2488	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [X] 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: [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME Tekturna-HCT (Aliskiren/Hydrochlorothiazide)	6. USER FEE I.D. NUMBER PD3007115

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, G, AND COSMETIC ACT BEFORE 9/1/92 (Self inatory)

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

HE 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 COMMERCIALLY

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

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewinginstructions, 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	TITLE	DATE
M. Kuhlmeier	Sr VP DRA	2/28/07

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$896,200.00

Form FDA 3397 (12/03)

Close Print Cover sheet

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 75,176

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

We also refer to your amendment dated December 19, 2006 (serial # 015), containing questions to obtain further scientific advice in preparation for an NDA submission.

We have completed the clinical, clinical pharmacology and statistical reviews of your submission and have the following comments.

1. Study CRD07 (short-term open-label study- 23 patients in the efficacy safety population) was included in aliskiren monotherapy NDA (21-985). It contained the combination treatment of aliskiren/HCTZ, and was conducted by Speedel, the original aliskiren monotherapy IND sponsor. The composition of the aliskiren clinical service forms (CSF) used in this study was different from the market formulation (MF) and final market image formulation (FMIF) that Novartis ultimately developed and used in the Phase III pivotal efficacy and safety studies. As a consequence, the pre-NDA briefing book proposed NOT to pool the results of the study, but provide the study report for this trial (and no datasets or CRTs) in the NDA submission. The pre-NDA written response from the Cardio-Renal Division confirms concurrence on our proposal not to pool the results of this trial. Does the Division agree that the submission of the SAS database for this trial is acceptable and submission of the CRTs is not required?

Response: We agree that SAS datasets are acceptable, however, please also submit the derived SAS datasets.

2. The pre-NDA written response from the Cardio-Renal Division requests that Novartis "submit patient narratives for deaths, serious adverse events (SAEs), and other significant AEs." The collection of regular adverse events in clinical trials does not usually provide sufficient information for narratives. As a consequence, Novartis proposes to limit the narratives to deaths and other serious adverse events. Does the Division agree that narratives related to death and serious adverse events will be sufficient to support registration?

Response: We are unaware of a regulatory definition of "regular" adverse events. Our request for AEs for which narratives are to be submitted is based on ICH E3. In the aliskiren NDA submission for hypertension we found that the information collected on significant AEs, such as those suggestive of angioedema, was inadequate. If you are not collecting adequate information to produce narratives on significant AEs, then we suggest modifying your collection procedures. While narratives are an ICH specification, U.S. regulations are more specific on the submission of CRFs and we find them to be more useful than narratives. Please comply with our requests regarding CRFs in the preliminary response letter

dated September 21, 2006. However, neither narratives nor CRFs are adequate if the information collection is inadequate.

3. The pre-NDA written response from the Cardio-Renal Division confirms agreement with submitting the planned NDA for aliskiren/hydrochlorothiazide with cross reference to relevant components in the previously submitted NDA for aliskiren monotherapy NDA (21-985). Several responses to FDA requests contained relevant clinical study reports, case report forms (CRFs), patient narratives, and SAS datasets. It is Novartis' understanding that cross-referencing these relevant responses submitted to NDA 21-985 is also acceptable. Does the Division agree that this is acceptable?

Response: Yes.

4. The pre-NDA written response from the Cardio-Renal Division requests that Novartis "send compositional tablets for all four strengths being developed and for the formulation used in Study CRD07." Does the Division prefer to receive the requested information when available or as a component of the official NDA submission?

Response: The compositional tables can be sent with the official NDA. We remind you that lot and batch numbers with batch sizes information should be sent as well to include tables cross-referencing which batches were used specifically.

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

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
1/16/2007 08:08:58 AM

DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

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

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

Transmitted to FAX Number:	973-781-3590
Attention:	Dr. Kimberly Dickerson
Company Name:	Novartis Pharmaceuticals Corporation
Phone:	862-778-4576
Subject:	IND 75,176, Pre-NDA September 21, 2006 Preliminary Responses
Date:	
Pages including this sheet:	

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

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

FDA Division of Cardiovascular and Renal Products Preliminary Responses

Sponsor:	Novartis Pharmaceuticals Corporation
Drug:	aliskiren/hydrochlorothiazide
IND:	75,176
Date of request:	July 6, 2006
Date request received:	July 7, 2006
Date of confirmation:	July 20, 2006
Date of pre-meeting:	September 6, 2006
Date of meeting:	September 21, 2006
Time:	9:00 – 10:30 am (tele-conference)
Date of meeting:	September 21, 2006 (sponsor requested a.m. meeting)
Type/Classification:	B/Pre-NDA
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting recorder:	John David

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products, HFD-110
Ellis Unger, M.D.	Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Ququan Liu, Ph.D.	Statistician, HFD-710
Lydia Velazquez, Pharm. D	Clinical Pharmacology, HFD-860
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Kasturi Srinivasachar, Ph.D.	Chemistry Pharmaceutical Assessment Lead, ONDQA
John David	Regulatory Health Project Manager, HFD-110

Background:

Aliskiren/hydrochlorothiazide, a fixed combination product which is currently being investigated in phase 3 studies for the proposed indication of treatment of hypertension. The sponsor referenced the pre-IND meeting on March 30, 2005 (minutes letter dated April 19, 2005) where the extensive development program for aliskiren/hydrochlorothiazide was agreed upon. Novartis plans to submit a New Drug Application for the fixed combination of aliskiren and HCTZ, as second line therapy, in the first quarter of 2007.

This Pre-NDA meeting was requested to address some issues relating to the NDA, and to gain concurrence on the proposed strategy for pooling efficacy and safety data and the general format of the NDA. The purpose of this meeting is to seek the Division's input and comments on the data presentation and formatting of the NDA. The NDA will make reference to clinical safety and efficacy data for the combination in the pending NDA 21-985 for rasilez (aliskiren).

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 21, 2006 between Novartis and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact John David), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact John David to discuss the possibility of including these for discussion at the meeting.

Questions for the Division:

Regulatory

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

Preliminary Response: The Division agrees with the request for a waiver of the pediatric requirement.

Labeling

2. We proposed draft labeling for the combination product as noted in Section 2.3. It is proposed that this combination product be used when a patient's blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide alone. This labeling is entirely consistent with the approved labeling for other antihypertensive combination products. Does the agency have any comments on the proposed labeling?

Preliminary Response: The usual phrase "alone or in combination with other antihypertensives" may be subject to modification depending upon the conclusions of our review of the aliskiren monotherapy NDA. Also, the labeling must be consistent with the Final Rule regarding labeling, including providing a highlights section.

3. We propose to submit the container packaging and components containing the proposed tradename logo, text, type, and size within 4 months (120 days) of the NDA submission. Does the Division agree with the proposal for the submission of packaging and components without an effect on the action date or overall review of the application?

Preliminary Response: The Division agrees with the proposal for the submission of packaging and components without an effect on the action date or overall review of the application.

Clinical/Statistical

4. Does the Division agree with our proposed pooling strategy for trials included in the SCS and SCE?

Preliminary Response: The Division agrees with the proposal for the pooling strategy for trials included in the SCS and SCE.

5. Does the Division agree with our proposal for patient narratives?

Preliminary Response: Please submit patient narratives for deaths, serious adverse events (SAEs), and other significant AEs. Please follow regulations for case report forms (CRFs), and submit CRFs for deaths and discontinuations. In addition, please submit CRFs for all strokes, transient ischemic attacks, and other suspected or investigator-reported cerebrovascular ischemic events, as well as for upper body edema or swelling, regardless of whether the event meets the regulatory definition of an SAE or results in discontinuation. Please include all clinical communications regarding a patient, regardless of whether the form is labeled a "CRF," e.g., include Medwatch-type SAE reporting forms. Please organize all forms for a patient contiguously in the submission.

6. Does the Division agree with our proposal NOT to pool results of the study (Study CRD07) conducted by Speedel (previous aliskiren monotherapy IND sponsor) and the study conducted in Japan (Study 1202)?

Preliminary Response: The Division agrees with the proposal NOT to pool results of the study (Study CRD07) conducted by Speedel (previous aliskiren monotherapy IND sponsor) and the study conducted in Japan (Study 1202), as long as the data are provided.

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

Preliminary Response: The Division agrees with the proposal to submit an integrated summary of laboratory data in International Units.

General

8. Does the Division agree with the general approach of submitting the planned NDA for a combination with cross reference to relevant components (i.e. study reports, patient narratives, case report forms, and SAS datasets) in our previously submitted NDA 21-985 for Rasilez?

Preliminary Response: The Division agrees with the proposal of submitting the planned NDA for the combination with cross reference to relevant components in the previously submitted NDA 21-985 for Rasilez (i.e., study reports, patient narratives, case report forms, and SAS datasets). Please ensure that the study numbers and titles can be linked and referenced to each other.

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

Additional Comments:

Clinical Pharmacology

1. A biowaiver request seems appropriate for the lowest strength since it is compositionally proportional to the highest strength of the proposed combination. Upon reviewing F2 similarity comparisons for the lowest strength, a biowaiver will be determined at that time.
2. Please send compositional tables for all four strengths being developed and for the formulation used in study CRD07.

Statistical

1. Please submit SAS transport analysis datasets and SAS analysis programs used for the final efficacy analyses in the NDA.

Meeting recorder: _____
John David

Meeting concurrence: _____
Norman Stockbridge, M.D., Ph.D.

Draft: jd/9-6-06
Final: jd/9-8-06

RD:
Liu 9/6/06
Srinivasachar 9/7/06
Resnick 9/7/06
Velazquez 9/6/06
Marciniak 9/7/06
Unger 9/8/06
Stockbridge 9/8/06

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/s/

Norman Stockbridge
9/8/2006 02:57:58 PM

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

Transmitted to FAX Number:	973-781-3590
Attention:	Kimberly Dickerson, Pharm.D.
Company Name:	Novarits Pharmaceuticals Corporation
Phone:	862-778-4576
Subject:	Teleconference Minutes
Date:	July 28, 2004
Pages including this sheet:	5

From:	**Daryl Allis**
Phone:	**301-594-5309**
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 Teleconference

Date of Meeting:	July 12, 2004
IND Application:	62,976
Drug:	Aliskiren (SPP-100) Tablets
Sponsor:	Norvartis Pharmaceuticals Corporation
Request Date:	June 24, 2004
Sponsor Notified:	June 25, 2004
Confirmation Date:	June 25, 2004 (fax)
Package Received:	July 1, 2004
Meeting Type:	A
Classification:	Special Protocol Response
Purpose:	Clarify the Division's responses to the Special Protocol Assessment
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, HFD-110
Shari Targum, M.D.	Acting Team Leader, Medical Officer, HFD-110
Lydia Velazquez, Pharm.D.	Clinical Pharmacologist & Biopharmaceutist, HFD-860
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Daryl Allis, 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
Martin Lefkowitz, M.D.	Executive Director, Clinical Research & Development
Catherine Schreiber, R.Ph., M.A.	Executive Director, Project Management
Sujata Vaidyanathan, Ph.D.	Sr. Lead Pharmacokineticist, Early Clinical Development
Steven Zelenkofske, D.O.	Director, Clinical Research and Development
Jin Zhu, Ph.D.	Associate Director, Biostatistics

Background

Novartis Pharmaceuticals Corporation (Novartis) 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 a potent and selective inhibitor of human renin, the enzyme responsible for the production of angiotensin I. Novartis submitted a request for Special Protocol Assessment on April 19, 2004 for their Phase 2 clinical protocol entitled "An 8 week double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension." The Division provided a Written Response dated June 3, 2004. Novartis requested this Type A meeting to clarify further

62,976 Aliskiren
SPA T-con 7/12/04
issues related to persistence of antihypertensive effect, lack of rebound effect, and their plans to address the Division's recommendations regarding the statistical analysis plan, dose response and pharmacokinetics of aliskiren and hydrochlorothiazide.

Topics for Discussion

Persistence of Antihypertensive Effect and Lack of Rebound Effect
Novartis noted that the End-of-Phase 2 minutes stated that a randomized withdrawal would be descriptive for persistence effect, and the Division's Written Response to the Special Protocol Assessment stated that the persistence of antihypertensive effect must be documented as well as the lack of a rebound effect. Novartis asked whether a randomized withdrawal study would be required for registration. Dr. Stockbridge stated we need evidence that the drug is effective weeks after patients have been on the drug and the cleanest way to get this information is from a randomized withdrawal study following 6-12 months of therapy. Novartis asked if they could show the persistent effect by adding the randomized withdrawal to an open label safety study. The Division agreed.

Novartis indicated that if the randomized withdrawal would be required, they planned to perform ambulatory blood pressure monitoring (ABPM) 2 weeks after withdrawal of therapy in those patients who had 24-hour ABPM recorded at baseline and at least once during the core double blind active treatment phase of the study and cuff blood pressure recordings and adverse events would be evaluated at weeks 1, 2, and 4 following abrupt withdrawal. Dr. Stockbridge stated that we were not sure whether the ABPM needed to be measured or when it should be measured in addition to the cuff blood pressures. The Division agreed the cuff blood pressures at 1, 2, and 4 weeks as described above would be adequate.

Novartis noted that not all drugs have done randomized withdrawal studies and they asked if this was a "first in a class" issue. Dr. Stockbridge agreed that the "n^{th}" drug in a class might not have done randomized withdrawal studies and concurred that being "first drug in a class" carries additional responsibilities.

Statistical Analysis
The Division agreed to the proposed statistical plan. Dr. Hung confirmed that Novartis still planned to use ANCOVA for the primary analysis for aliskiren and hydrochlorothiazide. He suggested that if there is no treatment by treatment interaction, then the ANCOVA without the treatment by treatment interaction term is a better analysis. He recommended that if there is a suspicion of treatment by treatment interaction, they consider the average (AVE) test. He said that from his experience, this test seems more powerful than the maximum (MAX) test.

Dose Response
Dr. Stockbridge noted the Division had previously recommended that Novartis consider testing aliskiren at 600-mg or higher to adequately describe the dose response. Novartis stated that the dose response would be further characterized in an additional study as previously recommended by the Division. The Division agreed.

Pharmacokinetics
Novartis stated the pharmacokinetics (PK) of aliskiren and hydrochlorothiazide would be evaluated in other studies because of sampling handling difficulties (plasma samples have to be centrifuged under refrigerated conditions and have to be kept frozen at $\leq$ -70°C prior to shipping). They believe their additional studies would fully characterize the PK rather than including sparse sampling in the proposed Phase 2 study. The Division agreed but suggested Novartis might consider collecting the PK sparse sampling at 1 or 2 sites that had the capabilities for proper sample handling as an alternative.

Conclusions/Recommendations

- Novartis agreed to conduct the randomized withdrawal study as discussed above.
- The Division recommends that ANCOVA should be used for testing the primary endpoints and the AVE test should be used if a large negative aliskiren-by-hydrochlorothiazide interaction is detected to assess the global assessment of combinations versus their respective monotherapies.

Meeting Recorder: *(See Appended Electronic Page)*
Daryl Allis, M.S., F.N.P.

Concurrence Chair: *(See Appended Electronic Page)*
Norman Stockbridge, M.D., Ph.D.

Draft	07/14/04	Final	07/27/04
RD:			
Hung	07/15/04		
Velazquez	07/23/04		
Targum	07/23/04		
Stockbridge	07/23/04		

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/s/

Daryl L. Allis
7/28/04 11:30:18 AM
A copy of the minutes will be faxed to
the sponsor after Dr. Stockbridge's final signature.

Norman Stockbridge
7/28/04 03:42:06 PM

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.
Assistant Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

We 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 April 19, 2004, request, serial number 027, for a special clinical protocol assessment, received April 21, 2004. The protocol is entitled "An 8 week double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren alone and in combination with hydrochlorothiazide in patients with essential hypertension."

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

Statistical:

1. For the analysis of the second primary objective (combination treatment), the proposed ANCOVA analysis seems to be reasonable if there is no large treatment by treatment interaction. The pattern of the interaction needs to be examined for the cells of nonzero dose combinations of the 4 by 4 factorial design, in addition to the test of the aliskiren-by-HCTZ interaction. If large treatment by treatment interactions are suspected, then some type of global assessment of dose combinations versus their respective components are needed (e.g. Hung, Chi & Lipisky, 1993, Biometrics). The protocol needs to propose an approach to global assessment.

2. You state that if the overall assessment of the combination treatment is positive, then the pairwise comparisons will be made by an ANCOVA model. The statistical test will be made at a 2-sided significance level of 0.05 for each comparison, and the combination dose is considered superior than monotherapy if the result is in favor of the combination. This is acceptable if these analyses are exploratory in nature. If you are seeking a claim for a specific dose, then a statistical approach needs to be proposed to control the total type I error rate at 0.05 level for all the pairwise comparisons involved.

In addition, we have the following comments.

Medical:

1. The dose range of aliskiren must be delineated. If bridging bioequivalence studies for the phase 2 study formulations are not done, then 600mg and possibly a higher dose should be included in the pivotal trials as recommended in the End-of Phase 2 (EOP2) meeting held on February 11, 2004.

2. The bioavailability of aliskiren is highly variable. The effects of this variability would be expected to be greater at peak than at trough. There have been reports of Serious Advent Events (SAEs) of hypotension in the clinical studies. The BP response must be characterized throughout the interdosing interval and should be correlated with drug levels.

3. Persistence of antihypertensive effect must be documented, as well as the lack of a rebound effect. This could be done through a randomized withdrawal following the primary endpoint determination in one of the trials as recommended at the EOP2 meeting.

Clinical Pharmacology & Biopharmaceutics

1. The protocol did not include pharmacokinetic (PK) and/or pharmacodynamic (PD) assessments. The interaction between aliskiren and hydrochlorothiazide could be evaluated in this study by using a sparse sampling approach.

2. In the presence of an adverse event, it is recommended that a blood sample for aliskiren assay be collected as close as possible to the occurrence of the adverse event.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

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

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
6/3/04 08:18:44 AM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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1451 Rockville Pike
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Transmitted to FAX Number:	973-781-3590
Attention:	Kimberly Dickerson, Pharm.D.
Company Name:	Novarits Pharmaceuticals Corporation
Phone:	862-778-4576
Subject:	Meeting Minutes
Date:	03/04/04
Pages including this sheet:	7

From: **Daryl Allis**
Phone: **301-594-5309**
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 an End-of-Phase 2 Meeting

Date of Meeting:	February 11, 2004
IND Application:	62,976
Drug:	Aliskiren (SPP-100) Tablets
Sponsor:	Norvartis Pharmaceuticals Corporation
Request Date:	December 23, 2003
Sponsor Notified:	January 5, 2005 (telephone)
Confirmation Date:	January 6, 2004 (fax)
Package Received:	January 15, 2004
Meeting Type:	End-of-Phase 2
Classification:	B
Purpose:	Discuss the Phase 3 development plan to support approval
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Daryl Allis

FDA Participants

Robert Temple, M.D.	Director, Office for Drug Evaluation I
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Karen Hicks, M.D.	Medical Officer, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacologist, HFD-860
Angelica Dorantes, Ph.D.	Clinical Pharmacologist, HFD-860
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HDF-110
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Novartis Participants

Martin Bedigian, M.D.	Director, Clinical Research & Development
Adrian Birch	Executive Director, Drug Regulatory Affairs
Yann Tong Chiang, Ph.D.	Director, Biostatistics
Kimberly Dickerson, Pharm.D.	Assistant Director, Drug Regulatory Affairs
Martin Lefkowitz, M.D.	Executive Director, Clinical Research & Development
Ian Michael Nicholls, B.Sc.	Registered Toxicologist, Toxicology/Preclinical Safety
Catherine Schreiber, R.Ph., M.A.	Executive Director, Project Management
Sujata Vaidyanathan, Ph.D.	Sr. Lead Pharmacokineticist, Early Clinical Development
Daniel Wasmuth	Chemical and analytical Development
Steven Zelenkofske, D.O.	Director, Clinical Research and Development

62,976 Aliskiren
EOP 2

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. Angiotensin I is converted by angiotension converting enzyme (ACE) to angiotensin II, one of the most potent known vasoconstrictors. Blocking renin prevents the production of angiotension peptides by the renin-ACE pathway. Renin inhibitors block the renin-angiotensin system (RAS) at a higher level in the cascade than ACE inhibitors and have a different effect on the components of the RAS. After the administration of a renin inhibitor the formation of both angiotensin I and II is blocked, thereby preventing the formation of angiotensin peptides by ACE and non-ACE pathways. These effects on the RAS provide the pharmacologic rationale for renin inhibition in the treatment of hypertension. Novartis plans to develop a film-coated tablet formulation containing [redacted] 150 and 300 mg, respectively. b(4)

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 between the Division and Speedel Pharmaceuticals include:
Pre-IND meeting, November 8, 2000
Pre-IND CMC meeting November 9, 2000

Novartis Pharmaceuticals Corporation requested this meeting to obtain Agency feedback on the clinical development program to support approval of Aliskiren. They are seeking the Agency's acceptance of Phase III programs which would establish Aliskiren as an effective and safe antihypertensive agent:
As a monotherapy, and as a free-add on agent in combination with other antihypertensive agents
As a fixed combination with hydrochlorothiazide

Topics for Discussion

Chemistry, Manufacturing and Controls
Dr. Srinivasachar noted that one of the intermediates in the manufacturing process contains a [redacted]. He asked whether this was carried over to the drug substance. [redacted] are known genotoxic carcinogens; therefore, Novartis needs to develop an assay to measure residual amounts of the [redacted] intermediate in the drug substance to provide assurance that this compound is not present even in trace amounts (less than [redacted]. b(4)

Renin Activity Suppression and Comparative Drugs
Dr. Temple noted that Aliskiren has a half-life of approximately 24 hours. He asked Novartis to explain why the plasma renin activity was not suppressed after 24 hours post administration. They stated that the initial dose did not suppress the renin activity for 24 hours but with repeated doses they found it was suppressed by day 8.

[redacted] b(4)

QT Effects
Novartis stated they have a negative signal for QT effects in their present studies. They, however, are planning to do a thorough, definitive QT study with a placebo and active control in healthy volunteers in accordance with the Guidance, and they will submit these data with the NDA. Dr. Throckmorton stated that if Novartis uses a positive control and the results are negative, they do not need to collect additional ECGs during the clinical trials for further QT evaluation.

Pediatric Studies
Novartis requested a deferral for pediatric studies. Dr. Throckmorton stated that a deferral would be acceptable on the basis that we need additional adult data before we could write an adequate Written Request to study Aliskiren in the pediatric population. Mr. Allis, Project Manager, will provide the sponsor with the appropriate regulatory pathway forward for granting a deferral for pediatric studies.

Preclinical study program

1. **Does FDA agree that the completed and planned preclinical study program is sufficient to support registration?**

Novartis will be starting a dose ranging study for a transgenic mouse carcinogenicity study next week and they will submit a Special (carcinogenicity) Protocol Assessment request when completed. The results of a 90-day dose range-finding study and a carcinogenicity study protocol for a two year study in rats went to the Executive Carcinogenicity Advisory Committee in May 2003.

The Agency agrees that the completed and planned preclinical study program would be sufficient to support registration.

Clinical pharmacology and pharmacokinetic study program

2. **Does FDA agree that the data obtained from the DDI studies using 150 mg are adequate for addressing DDI label information given that the therapeutic doses in the phase III program will be between 75 and 300 mg?**

Yes, but in vitro metabolic studies showing that Aliskiren is not a substrate of CYP450 and does not induce/inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, and the possibility of having metabolic drug interactions with other drugs cleared by the above isoenzymes is unlikely. Therefore, some of the newly proposed DDI studies may not be needed, with the exception of HCTZ that will be used in the proposed combination therapy.

Additionally, if the currently ongoing in vitro P-glycoprotein study shows that Aliskiren inhibits and/or is a substrate of P-glycoprotein, additional in vivo DDI studies would be needed.

3. **Does FDA agree that Novartis is not required to further demonstrate comparability between the Phase 2 and the Phase 3 formulation?**

The provided information shows that the formulations do not meet the SUPAC criteria for a biowaiver. If this is correct, then dissolution data alone cannot be used to support the link between the Phase 2 and Phase 3 (to-be-marketed) formulations. Dr. Marroum explained that if they had a greater than a 10% difference in total excipients between the two formulations they would need a bioequivalence study. The formulation data provided in the meeting package appears to be in excess of 10%. They would need to link the formulation used in the Phase 2 study to the formulation they plan to market and use in the Phase 3 study if they plan to use the data from the Phase 2 study in determining safety and efficacy.

The sponsor stated that they would reassess their formulation comparability to determine whether they are a level 1 or 2, as referred in the Guidance and present a case for not needing a bioequivalence (BE) study. If they determine they are a level 3, they understand that they would need a BE study.

Dr. Temple suggested that they could consider adding a 600-mg Aliskiren dose to the Aliskiren/ Valsartan and the Aliskiren/ hydrochlorothiazide (HCTZ) studies rather than linking the to-be-marketed formulation to the Phase 2 studies. If this course is taken, then the sponsor will have the full range of doses explored using the to-be-marketed formulation, along with the earlier study to be used as confirmatory evidence.

[redacted] b(4)

[redacted] b(4)

[redacted] b(4)

[redacted] b(4)

8. **Does FDA agree that the proposed safety database is of adequate scope for approval of a new chemical entity in hypertension (number and duration of patient exposures, and number of exposures at each dose)? Extended exposure to 75 mg of Aliskiren as monotherapy is not anticipated. Is the anticipated exposure to 150 mg and 300 mg both alone and in combination with hydrochlorothiazide (HCTZ) sufficient to support registration of all [redacted] doses?** b(4)

The Agency agrees.

9. **Does the FDA agree that the proposed study design (A2303) in patients with severe hypertension satisfies the requirements for the evaluation of severe patients? Does FDA agree with the definition of severity as defined by Novartis?**

The Agency does not separate out severe, moderate or mild hypertension. To date, antihypertensive agents that work in one surely have worked in all hypertension and the labeling would support the use with hypertension generally.

10. **Does FDA agree that clinical efficacy and safety data in the elderly can be provided by analyzing the subset of elderly patients in our total clinical database?**

The Agency agrees.

11. **Does FDA agree that the multifactorial design study A2204 evaluating various combinations of Aliskiren with HCTZ can be considered a single, pivotal efficacy trial for the approval of an NDA for a fixed-dose combination of Aliskiren with HCTZ? (Please note that this trial will also serve as a pivotal trial for the registration of Aliskiren monotherapy and support registration of Aliskiren for use in [redacted] with HCTZ.)** b(4)

The Agency agrees, with the addition of appropriate PK data.

Regulatory

12. Does FDA agree that the data package of previous, ongoing and proposed studies, if successful, will support approval of the proposed indication: - "Aliskiren is indicated for the treatment of essential hypertension? It may be used alone or in combination with other antihypertensive agents?" Does FDA agree that the data package of previous, ongoing and proposed studies, if successful, would support approval of our desired labeling (see Appendix 3)?

The Agency agrees, but we generally do not include in the labeling.

Conclusions/Recommendations

The Division recommends the sponsor consider the following:

- Contact the Division for further discussions regarding the CMC issues
- Submit a Special Protocol Assessment Request for the Transgenic mouse study when available
- Submit a [redacted]
- Submit a proposed statistical analysis plan for review
- Conduct the studies to characterize the PK/PD and P-glycoprotein transport fully and request additional conversation with Dr. Marroum

b(4)

The Division will contact the sponsor and provide a regulatory pathway for requesting a deferral for pediatric studies.

Meeting Recorder: Daryl Allis, M.S., F.N.P.

Concurrence Chair: Robert Temple, M.D.

Draft	02/13/04	Final	03/04/05
RD:			
Srinivasachar	02-13-04		
Resnick	02/13/04		
Hung	02-13-04		
Dorantes	02-13-04		
Marroum	02/18/04		
Hicks	02/18/04		
Marciniak	02/19/04		
Throckmorton	02/24/04		
Temple	03/01/04		

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

/s/

Daryl L. Allis
3/4/04 09:45:50 AM
A copy of the minutes will be faxed to
the sponsor following Dr. Temple's concurrence and signature.

Robert Temple
3/4/04 07:00:11 PM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 22-107	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Tekturna HCT Tablets Established Name: aliskiren/hydrochlorothiazide Dosage Form: 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg		Applicant: Novartis Pharmaceuticals Corporation	
RPM: John David		Division: DCaRP	Phone # 301-796-1059

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

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.

☐ Confirmed ☐ Corrected
Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	1/20/08
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): 4

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

☐ Orphan drug designation

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

NDAs and NDA Supplements:
- ☐ OTC drug

Other:

Other comments:

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

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

notice of certification?

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

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

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

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

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

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

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

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	Division Director 1/XX/08
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	1/15/08
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	1/16/08
• Original applicant-proposed labeling	3/20/07 & 12/18/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Avalide, Azor
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	1/15/08
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	1/16/08
• Original applicant-proposed labeling	3/20/07 & 12/18/07
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide	N/A
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	11/29/07
• Most recent applicant-proposed labeling	12/11/07
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 12/21/07 ☐ DSRCS ☒ DDMAC 1/2/08 ☒ SEALD 1/8/08 ☒ Other reviews DRM PPI review 1/2/08 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	5/16/07
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	 N/A N/A
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	N/A
• Incoming submission documenting commitment	N/A
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	11/29/07, 11/21/07, 5/24/07, 4/5/07
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 9/8/06 (IND 75,176, Preliminary Responses, see also 1/16/07 advice letter)
• EOP2 meeting *(indicate date)*	☐ No mtg 2/11/04 (under IND 62,976)
• Other (e.g., EOP2a, CMC pilot programs)	SPA 6/3/04 (tcon 7/12/04)
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	N/A
• 48-hour alert or minutes, if available	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	1/7/08 (2), 11/20/07, 4/26/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See page 72 of 11/20/07 CMC Review
• ☒ Review & FONSI *(indicate date of review)*	See page 72 of 11/20/07 CMC Review
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	See page 72 of 11/20/07 CMC Review
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	N/A ☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 10/19/07 ☒ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	N/A ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	8/31/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	12/7/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	See page 24 of Clinical Review
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	See page 17 of Clinical Review
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	10/9/07 OSE
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
• Clinical Studies	N/A
• Bioequivalence Studies	N/A
• Clin Pharm Studies	N/A
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 10/4/07
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 12/13/07