

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022545Orig1s000

OTHER REVIEW(S)

Division of Cardio-Renal Drug Products
Consultation for Division of Drug Marketing, Advertising, and Communications

From: Shen Xiao, M.D., Ph.D. Medical Officer
Division of Cardiovascular and Renal Products
Through: Norman Stockbridge, M.D., Ph.D. Division Director
Division of Cardiovascular and Renal Products
To: Emily Baker, Pharm.D.
Regulatory Review Officer
Division of Drug Advertising, Marketing, and Communications (DDMAC)

Subject: NDA 22-545
Name of Drug: Tekamlo (aliskiren and amlodipine)
Formulation: Oral tablets
Related Applications: N/A
Approved Indications: Treatment of hypertension
Sponsor: Novartis

Documents Used for Review: Tekamlo [redacted] (b) (4)
from the Sponsor

Consult assigned date: October 26, 2010
Desired completion date: November 17, 2010
Consult completed date: November 2, 2010

Background Information: The Sponsor (Novartis) has submitted [redacted] (b) (4)
for Tekamlo (aliskiren and amlodipine) tablets [redacted] (b) (4)

[redacted] (b) (4)

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/s/

SHEN XIAO
11/02/2010

NORMAN L STOCKBRIDGE
11/02/2010

Project Manager Overview

**NDA 022545
TEKAMLO (aliskiren/amlodipine) Tablets (150/5, 150/10, 300/5, 300/10 mg)**

Background:

This NDA was submitted pursuant to section 505(b)(2) of the FD&C act on October 29, 2009 for four fixed dose combinations of aliskiren and amlodipine, (150/5, 150/10, 300/5, 300/10 mg). The sponsor seeks approval for the treatment of hypertension as initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals and in patients not adequately controlled with monotherapy. This drug combination was the subject of two INDs, IND 062976 for aliskiren monotherapy and IND 072407 for aliskiren/amlodipine fixed dose combination.

This application was reviewed by the Pediatric Review Committee (PeRC) on June 30, 2010 and granted a full waiver.

This application was discussed at an August 2, 2010 505(b)(2) clearance meeting and cleared for action from a 505(b)(2) perspective.

NDA Reviews and Memos

Division Director's Memo

Dr. Norman Stockbridge; August 16, 2010

In his review Dr. Stockbridge conveys the Division's decision to issue an Approval letter for Tekamlo for hypertension.

CDTL Memo

Dr. Thomas Marciniak; August 9, 2010

Recommended Action: Approval

See review for details.

Clinical Review; July 7, 2010

Dr. Shen Xiao

Recommended Action: Approval

See review for details.

Statistical Review; June 2, 2010

Dr. Valeria Freidlin

In her review, Dr. Freidlin indicated that there are no statistical issues with the NDA and that she agreed with the statistical methods used by the sponsor.

Clinical Pharmacology; June 16, 2010, amended July 21, 2010

Dr. Divya Menon-Anderson

Recommended Action: Approval

Dr. Menon-Anderson recommended approval from a clinical pharmacology standpoint. In the amendment to her review Dr. Menon-Anderson added additional information relating to her review of possible pharmacokinetic drug interactions between aliskiren and amlodipine. The

022545 Tekamlo (aliskiren/amlodipine)

conclusion of this review was that the combination of amlodipine and aliskiren was considered to be well tolerated and safe.

Pharmacology Review; June 3, 2010

Dr. Gowra Jagadeesh

Recommended action: Approvable

Please see review for details.

Chemistry Review; June 9, 2010, amended August 4, 2010

Dr. Lyudmila Soldatova

Recommended action: Approval

In her review Dr. Soldatova

(b) (4)

recommended approval of the 10-count blister pack. Her overall recommendation was for approval.

The overall recommendation from the Office of Compliance was Acceptable, (April 27, 2010)

Consult/Other Reviews:

DMEPA

Dr. Kristina Arnwine – August 25, 2010

Trade Name

Dr. Tselaine Jones-Smith, February 2, 2010

Dr. Kristina Arnwine, August 12, 2010 (Pre-Action review) Acceptable

MHT

Dr. Jeanine Best, August 2, 2010

SEALD

Dr. Debra Beitzell, July 27, 2010

DRISK

Dr. Steve Morin, July 22, 2010

DDMAC

Dr. Emily Baker, July 16, June 11, 2010

DSI

Dr. Sripal Mada, July 9, 2010

Environmental Assessment

Dr. Emily Mcvey, June 28, 2010

Biopharm

Dr. Tien Mien Chen, June 11, 2010

Action Items:

An approval letter will be drafted for Dr. Stockbridge's signature.

Michael Monteleone

August 26, 2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

MICHAEL V MONTELEONE
08/26/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 24, 2010

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Through: Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Kristina A. Toliver, PharmD, Team Leader
Division of Medication Error Prevention and Analysis

Subject: Labeling Review

Drug Name: Tekamlo (Aliskerin and Amlodipine) Tablets,
150 mg/5 mg, 150 mg/10 mg, 300 mg/5 mg and 300 mg/10 mg

Application Type/Number: NDA 022545

Applicant: Novartis Pharmaceuticals Corporation, Inc.

OSE RCM #: 2009-2184

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1 INTRODUCTION

This review responds to a request from the Division of Cardiovascular and Renal Products (DCRP) for DMEPA to review of the container labels, blister labels, carton labeling, insert labeling and patient labeling for Tekamlo from a medication error perspective.

2 REGULATORY HISTORY

DMEPA reviewed the labels and labeling submitted by the Applicant on February 25, 2010 and July 29, 2010 (See Appendices A through F). We provided recommendations on the container labels, blister labels, and carton labeling in order to minimize the potential for medication errors (See Appendix G). DCRP forwarded these recommendations to the Applicant on August 16, 2010. Subsequently the Applicant submitted revised container labels, blister labels and carton labeling on August 20, 2010. The revised labels and labeling and the February 25, 2010 insert labeling are the subject of this review.

3 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the container labels, blister labels, carton labeling, and insert labeling that were submitted on August 20, 2010. See Appendix A.

4 RECOMMENDATIONS

We acknowledge that the Applicant addressed all of the recommendations concerning the container labels, blister labels and carton labeling in their August 20, 2010 submission. However, we noted areas where information on the insert labeling can be clarified and improved upon to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1, *Comments to the Division*.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact OSE Project Manager, Nina Ton, at 301-796-2311.

4.1 COMMENTS TO THE DIVISION

1. Package Insert Labeling

A. General Comments

Include units of measure with each notation of strength throughout the insert labeling. Additionally, ensure that there is a space between the number and unit of measure throughout the labeling. For example, revise 150/5 and 150/5mg to read as 150 mg/5 mg.

B. Full Prescribing Information

In Section 3 (*Dosage Forms and Strengths*), the presentation of information in paragraph form makes this section difficult to read. In order to improve readability, revise the section into a bullet or number format that is easier to read. See Section 3 (*Dosage Forms and Strengths*) of Tekturna HCT (NDA 022107).

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Appendix G: Label and Labeling Comments regarding February 25, 2010 submission

COMMENTS TO THE APPLICANT

1. General Comments

- A. We note the color purple is used for the proprietary name across the Aliskerin product line (i.e. Tekturna, Tekturna HCT, and Tekamlo). Additionally, the same circle graphic is used across the product line. In order to adequately differentiate Tekamlo from the remaining Aliskerin products we recommend a different color be used for the proprietary name and the circle graphic be revised so that it is not the same across the product line.
- B. Present the entire proprietary name in a single font color. As currently presented, the use of two different colors for the “Tek” and “amlo” portions of the proprietary name make the name difficult to read.

2. Container Labels (30 count and 90 count)

See comments 1-A and 1-B.

3. Blister Labels

- A. Differentiate the product strengths through the use of color, boxing, reverse-blocking, or some other means.
- B. Include an asterisk at the beginning of the qualifying statement “each tablet contains... XX mg of amlodipine besylate” so that it is clear what the asterisk at the end of the product strength is referring to.

4. Unit-Dose Carton Labeling

- A. See comments 1-A and 1-B.
- B. We note different colors are used to differentiate the product strengths (e.g. (b) (4)), however, the color blue is still used predominantly in the labels and labeling thereby diminishing any differentiation offered by the differing colors. We recommend using the same colors used to differentiate the product strengths in place of where the color blue is used (e.g. the color band across the top of the carton labeling that contains the NDC number) as is used on the 30-count and 90-count proprietary container labels.
- C. Remove the (b) (4) statement. The “Contents: 10 blister cards of 10 tablets each” statement is a more accurate reflection of the contents of the carton.

5. Sample Blister Pack Labels (10-count)

- A. Revise the statement of strength to read “XX mg/XX mg per tablet” on all physician sample labels and labeling. As currently presented it may be difficult for patients and/or practitioners to determine if the product strength listed is contained in one tablet or the contents of the entire physician’s sample.
- B. The sample blister pack label for the 10-count packaging configuration submitted on July 29, 2010 differs from that of the (b) (4). The current 10-pack configuration does not illustrate how the tablets will be packaged in the blister. Please clarify how and why this 10-count blister pack label differs from (b) (4) (b) (4)

6. Sample Shell Pack Front Labeling

See comments 1-A, 1-B, and 5-A.

7. 6x10 Sample Packer Carton Labeling

A. See comments 1-A, 1-B, and 4-B.

B. Remove the (b) (4) statement. The “Contents: 6 blister packs (2x5) of 10 tablets each” statement is a more accurate reflection of the contents of the carton.

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NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

KRISTINA C ARNWINE
08/24/2010

DENISE P TOYER
08/25/2010

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-545
APPLICANT	Novartis Pharmaceuticals Corporation
DRUG NAME	TEKAMLO (aliskiren and amlodipine)
SUBMISSION DATE	October 29, 2009
SEALD REVIEW DATE	July 26, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

DEBRA C BEITZELL
07/27/2010
SEALD comments sent to DCRP on 7/26/10

LAURIE B BURKE
07/27/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 22 2010

To: Norman L Stockbridge, M.D., PhD., Director
Division of Cardiovascular and Renal Products (DCRP)

Through: Mary Willy, PhD., Deputy Director
Division of Risk Management (DRISK)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name(s): Tekamlo (aliskiren and amlodipine) Tablets

Application Type/Number: NDA 22-545

Applicant/sponsor: Novartis Pharmaceuticals Corporation

OSE RCM #: 2010-768

1 INTRODUCTION

This review is written in response to a request by the Division of Cardiovascular Renal Products (DCRP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Tekamlo (aliskiren and amlodipine) Tablets.

Novartis Pharmaceutical Corporations submitted an original New Drug Application, NDA 22-545, for Tekamlo (aliskiren and amlodipine) Tablets on October 29, 2009. Tekamlo is a direct renin inhibitor and dihydropyridine calcium channel blocker combination tablet. The proposed indication is for the treatment of hypertension:

- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals.
- In patients not adequately controlled with monotherapy.
- May be substituted for titrated components

The Applicant also submitted a Risk Management Plan in this original NDA. The Applicant states in their cover letter that they conclude routine pharmacovigilance activities are appropriate for this product.

Please let us know if DCRP would like a meeting to discuss this review or any of our changes prior to sending it to the Applicant. DRISK requests that DCRP copy us on the correspondence when the Review Division sends PPI comments and changes to the Applicant.

2 MATERIAL REVIEWED

- Draft Tekamlo (aliskiren and amlodipine) Tablet Prescribing Information (PI) submitted October 29, 2009, revised by the Review Division throughout the review cycle, and provided to DRISK July 09, 2010
- Draft Tekamlo (aliskiren and amlodipine) Tablet Patient Package Insert (PPI) submitted October 29, 2009, revised by the Review Division throughout the review cycle, and provided to DRISK July 09, 2010

3 RESULTS OF REVIEW

In our review of the MG and IFU, we:

- Referenced the language regarding cardiovascular outcomes based upon agreement with DCRP in relation to the DRISK review of the Coreg and Coreg CR PPI's, dated May 28, 2010, 2010, and further revised in the Complete Response letter dated June 10, 2010.
- ensured that the cardiovascular outcome statement in the MG are consistent with the Draft guidance for Industry Hypertension Indication: Drug labeling for Cardiovascular Outcome Claims, March 2008
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

This reviewer did not review the Risk Management Plan submitted by the Applicant. DCRP, please notify DRISK if you determine that there are serious risks that may warrant a Risk Evaluation and Mitigation Strategy (REMS) for Tekamlo (aliskiren and amlodipine) Tablets.

Our annotated PI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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/s/

STEVE L MORIN
07/22/2010

MARY E WILLY
07/22/2010
I concur

INTRODUCTION

Novartis submitted a New Drug Application (NDA) 22-545, on October 28, 2009, for Tekamlo (aliskiren and amlodipine) Tablets for the treatment of hypertension.

On July 9, 2010, the Division of Cardio-Renal Products (DCRP) consulted the Maternal Health Team (MHT) to review and comment on the proposed pregnancy and nursing mothers sections of labeling.

BACKGROUND

Tekamlo (aliskiren and amlodipine) Tablets

Tekamlo is a combination of aliskiren, a direct renin inhibitor that decreases plasma renin activity (PRA) and inhibits the conversion of angiotensinogen to form the inactive decapeptide angiotensin I (Ang I), and amlodipine, a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Based on mechanism of action, drugs that act directly on the renin-angiotensin-aldosterone system can reduce fetal renal function and increase fetal and neonatal morbidity and death when administered in the second and third trimester of pregnancy and potentially during the first trimester of pregnancy. Adverse fetal effects include oligohydramnios (associated with fetal lung hypoplasia, contractures, and skeletal deformities), hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Angiotensin II receptors are widely expressed in fetal tissue and could potentially play a role in fetal development.

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling under current regulations while new regulations complete the development and clearance process. This approach complies with current regulations, including the assignment of pregnancy categories, but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection are presented in an organized, logical format to make the information as clinically relevant as possible for prescribers. This includes describing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount, as this can vary significantly from species to species.

This review provides MHT’s suggested revisions to the proposed pregnancy and nursing mothers labeling for Tekamlo (aliskiren and amlodipine) Tablets.

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/s/

JEANINE A BEST
07/20/2010

Karen B FEIBUS
07/23/2010
I agree with the content and recommendations contained in this review.

LISA L MATHIS
08/02/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: July 16, 2010

To: Mike Monteleone – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Zarna Patel – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 022545 Tekamlo (aliskiren and amlodipine) tablets

DDMAC has reviewed the proposed product labeling (PI) and Patient Package Insert (PPI) submitted for consult to DDMAC on April 19, 2010, for Tekamlo (aliskiren and amlodipine) tablets (Tekamlo).

The following comments are provided using the updated proposed PI sent via email on July 8, 2010 by Mike Monteleone. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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/s/

EMILY K BAKER
07/16/2010

MEMORANDUM

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

DATE: July 09, 2010

TO: Norman Stockbridge, M.D., Ph.D.
Director, Division of Cardiovascular and Renal
Products, Office of Drug Evaluation (HFD-570)

FROM: Sripal R. Mada, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 7/9/10
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-545, Tekamlo®
(Aliskiren/Amlodipine) (150/5 mg, 150/10 mg, 300/5 mg,
300/10 mg, Sponsored by Novartis Pharmaceuticals
Corporation.

At the request of the Division of Cardiovascular and Renal Products (DCRP), the Division of Scientific Investigations (DSI) audited both the clinical and analytical portions of the following bioequivalence (BE) study:

CSPA100A2102: "An open-label, randomized, two treatment, two-period, single-dose, crossover study to determine the bioequivalence of fixed combination of SPA100 (aliskiren/amlodipine 300/10 mg oral tablet) and the free combination of aliskiren 300 mg market tablet and amlodipine 10 mg (2 X 5 mg tablets) in healthy adult subjects".

Inspection of the clinical portion was conducted at Lambda Therapeutic Research Limited, Plot # 38, Near Silver Oak Club, SG Highway, Gota, Ahmedabad 380 061, India (Lambda). Inspection of the analytical portion was conducted at [REDACTED] (b) (4)

Following the inspection of the clinical portion (June 7-10, 2010), Form FDA-483 was issued (**Attachment 1**). The firm's response (dated June 16, 2010) was received on June 24, 2010 by email attachment (**Attachment 2**).

Page 2 - NDA 22-545, Tekamlo (Aliskiren/Amlodipine) (150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg)

Following the inspection of the analytical portion (June 11-16, 2010), Form FDA-483 was issued (**Attachment 3**). The firm's response (dated July 07, 2010) was received on July 07, 2010 by email attachment (**Attachment 4**).

The observations for study CSPA100A2102, the 483 responses from Lambda and (b)(4), and our evaluations follow:

Lambda Therapeutic Research Limited, Ahmedabad, India

1. Failure to properly translate in Subject Consent Form (SCF).

Specifically, when translating from English to Gujarati, the boxes marked in English as "Please initial box" was changed to a check box requiring only a check, no longer requiring initials of the subjects. In spite of the mistake in translation, both documents, in English and Gujarati were approved by the Independent Ethics Committee (IEC).

Lambda acknowledged this observation, and stated in the response that they had communicated this error to the translator, who also admitted this mistake. Lambda confirmed that although both SCFs (English and Gujarati) were approved by IEC, only Gujarati version was used in entire consenting process of this study.

DSI finds this observation as having no impact on study data integrity, as only one version of SCF (Gujarati) was used for the entire study.

2. Failure to properly document the source records. (See Form FDA-483 (clinical) for complete observation).

Specifically Subjects 5108, 5118, 5119, 5125, 5146, 5150, 5155, 5189, 5195, and 5202 were marked in Source Data Form as 'Yes' to the question "Has the subject completed the study as per protocol?" These subjects however, failed to attend the ambulatory visits for blood sample collections scheduled between 72 and 168 hours.

DSI finds this observation has no impact on study data.

3. Failure to sign off 88 of 120 Source Data Form (SDF). (See Form FDA-483 (clinical) for complete observation).

The signed off by the Principle Investigator (PI) is needed to certify that data in the SDF are complete, correct, consistent and accurate. The sponsor verified that the electronic version

was signed off by the PI and this electronic signature certified the correctness of the data.

In their response, Lambda acknowledged that the PI should have signed off all the source data forms. Lambda also said that PI of this study is no longer associated with the organization.

DSI finds this observation should not have impact on study data.

(b) (4)

(b) (4)

1. Failure to select appropriate concentration for evaluating dilution linearity during validation.

Specifically, during validation, a 400 ng/mL concentration (2x ULOQ) was selected to evaluate x4 and x10 dilution (calibration range was 0.5 - 200 ng/mL). This is objectionable as about 139 subject plasma aliskiren concentrations were >400 ng/mL (see **Attachment 5**).

(b) (4) acknowledged this observation, and conducted an additional dilution linearity study using higher concentration (5x ULOQ), during the inspection. The new dilution linearity results, demonstrated that the sample dilution procedure used in this study has no effect for subject sample concentrations >400 ng/mL.

DSI has found that the newly submitted dilution linearity data is acceptable, and hence this observation will have no effect on study results.

2. Failure to follow SOP (SOP # VIN-BRD-016, Repeat Analysis) concerning a subject sample with significant pre-dose concentration.

According to the SOP, if the pre-dose plasma concentration of a subject is >5% of C_{max} , pre-dose sample of that subject in that dosing period should be repeated. However, in Subject # 0001_05205, the amlodipine pre-dose sample in period II was 5.45% of C_{max} , but the SOP was not followed.

During the inspection, (b) (4) provided a summary of all subject's pre-dose plasma concentrations that were exceeding LLOQ for both aliskiren and amlodipine (see **Attachment 6**). Per the data provided, 41 subjects in each group (aliskiren and amlodipine) had plasma pre-dose concentrations greater than LLOQ. The pre-dose amlodipine concentration in five subjects (Subjects #

Page 4 - NDA 22-545, Tekamlo (Aliskiren/Amlodipine) (150/5 mg, 150/10 mg, 300/5 mg, 300/10 mg)

0001_05129, 0001_05157, 0001_05176, 0001_05188, 0001_05205) were >2% of its C_{max} . (b)(4) acknowledged this observation, and said that the wash-out period between periods I and II was not long enough due to the long half-life of amlodipine.

As amlodipine pre-dose sample for Subject # 0001_05205 in period II was >5% of C_{max} , the accuracy of the data generated in this subject is questionable.

Conclusion:

Following the inspection, DSI concludes that:

- The amlodipine data in Subject # 0001_05205, period II cannot be assured due to significant pre-dose amlodipine concentration.
- The OCP reviewer should also assess data from subjects (Subjects # 0001_05129, 0001_05157, 0001_05176, 0001_05188) with pre-dose amlodipine concentrations >2% of C_{max} values.
- The remaining data from both clinical and analytical portions of study CSPA100A2102 can be accepted for review.

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



Sripal R. Mada, Ph.D.

Final Classification:

**VAI - Lambda Therapeutic Research Limited, Ahmedabad, India
(Clinical)**

FEI: 3005124764

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Page 5 - NDA 22-545, Tekamlo (Aliskiren/Amlodipine) (150/5 mg,
150/10 mg, 300/5 mg, 300/10 mg)

cc: DARRTS

DSI/GLPBB/Mada/Kaufman/Rivera-Lopez/Yau/Haidar/Ball/CF

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Draft: SRM 07/07/2010

Edit: MKY 07/08/2010

DSI: 6024; O:\Bioequiv\EIRCover\22545nov.tek.doc

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

SRIPAL R MADA

07/09/2010

Original signed documents are available in the DSI file.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: June 11, 2010

To: Mike Monteleone – Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

From: Emily Baker – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Mike Sauers – Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 022545 Tekamlo (aliskiren and amlodipine besylate) tablets

DDMAC has reviewed the proposed carton and container labeling for Tekamlo (aliskiren and amlodipine besylate) tablets (Tekamlo), submitted for consult on April, 19, 2010.

The following comments are provided using the updated proposed carton and container labeling sent via email on June 11, 2010 by Mike Monteleone. Comments on the proposed product labeling (PI) and patient labeling (PPI) will be sent separately when DDMAC receives the proposed labeling from the Review Division.

DDMAC has no comments on the proposed carton and container labels at this time.

If you have any questions about DDMAC's comments, please do not hesitate to contact me.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

EMILY K BAKER
06/11/2010

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

x Other (please explain):

The results of the bioequivalence (BE) study conducted at the site identified for inspection are important in linking the observed results from the pivotal clinical study to the to-be-marketed (TBM) dosage form.

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **March 01, 2010**. We intend to issue an action letter on this application by **August 29, 2010**.

Should you require any additional information, please contact Divya Menon-Andersen, Clinical Pharmacology Reviewer, (x63709) or Michael Monteleone, Regulatory Project Manager, (x61952).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22545	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	ALISKIREN/AMLODPINE(SPA 100A)FIXED COMBO

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/s/

MICHAEL V MONTELEONE
01/05/2010

NORMAN L STOCKBRIDGE
01/05/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022545 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Tekamlo Established/Proper Name: aliskiren/amlodipine Dosage Form: Tablets Strengths: aliskiren/amlodipine (150/5mg; 150/10mg; 300/5mg; 300/10mg)		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: 10/28/09 Date of Receipt: 10/29/09 Date clock started after UN:		
PDUFA Goal Date: 08/29/10		Action Goal Date (if different): 08/28/10
Filing Date: 12/27/09		Date of Filing Meeting: 12/9/09
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of hypertension		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 062976; IND 072407				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.			X	
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
 <i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X																		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).		X																		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>		X																		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:		X																		
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X																	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X																		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA</i> s only)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i> s/ <i>NDA</i> efficacy supplements) or under 21 CFR 601.2 (<i>BLA</i> s/ <i>BLA</i> efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>		X		
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>			X	

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 09-22-06 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 10-09-08 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): 10-30-07 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: 12-09-09

BLA/NDA/Supp #: 022545

PROPRIETARY NAME: TEKAMLO

ESTABLISHED/PROPER NAME: aliskiren/amlodipine

DOSAGE FORM/STRENGTH: 150/5mg; 150/10mg; 300/5mg; 300/10mg

APPLICANT: Novartis

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of Hypertension

BACKGROUND: Sponsor submitted new NDA 022545 on 10-29-09 for aliskiren/amlodipine tablets for the treatment of hypertension. Clinical investigations were conducted under IND 062976 (SPP100A-aliskiren monotherapy) and IND 072407 (SPA100A- aliskiren/amlodipine fixed dose combination).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael Monteleone	Y
	CPMS/TL:	Ed Fromm	Y
Cross-Discipline Team Leader (CDTL)	Thomas Marciniak		Y
Clinical	Reviewer:	Shen Xiao	Y
	TL:	Thomas Marciniak	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:	NA	

Clinical Pharmacology	Reviewer:	Divya Menon-Anderson	Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Valeria Freidlin	Y
	TL:	Jim Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gowra Jagadeesh	N
	TL:	Patricia Harlow	N
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Soldatova Lyudmila	Y
	TL:	Kasturi Srinivasachar	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	NA	
	TL:	NA	
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	NA	
	TL:	NA	
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments: Recommend inspection of Pivotal BE study</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

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<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Norman Stockbridge	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

An original application is likely to be a 505(b)(2) application if:

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22545

ORIG-1

NOVARTIS
PHARMACEUTICA
LS CORP

ALISKIREN/AMLODPINE(SPA
100A)FIXED COMBO

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

/s/

MICHAEL V MONTELEONE

12/23/2009