

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022545Orig1s000**

**CHEMISTRY REVIEW(S)**

## **NDA 22-545**

**Tekamlo (Aliskiren and Amlodipine) Tablets**

**Novartis Pharmaceuticals Corporation**

**Division of Cardiovascular and Renal products**

**Lyudmila N. Soldatova, Ph. D.**  
**DPAI/ONDQA**

**Review of Chemistry, Manufacturing, and Controls**

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# Chemistry Review Data Sheet

1. NDA 22-545
2. REVIEW #2
3. REVIEW DATE: August 04, 2010
4. REVIEWER: Lyudmila N. Soldatova
5. PREVIOUS DOCUMENTS:

Previous Documents

Original  
Review #1

Document Date

29-OCT-2009  
09-JUN-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment  
Amendment  
Amendment  
Amendment  
Amendment

Document Date

10-JUN-2010  
14-JUN-2010  
02-JUL-2010  
21-JUL-2010  
29-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation  
Address: One Health Plaza  
East Hanover, NJ 07936  
Representative: Lori Ann Kneafsey  
Associate Director, Drug regulatory Affairs  
Telephone: 862-778-5369

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tekamlo (proposed)
- b) Non-Proprietary Name (USAN): aliskiren fumarate/amlodipine besylate
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

## 10. PHARMACOL. CATEGORY: Hypertension

## 11. DOSAGE FORM: Tablets

## 12. STRENGTH/POTENCY: 150/5 mg, 150/10 mg, 300/5 mg, and 300/10 mg,

## 13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

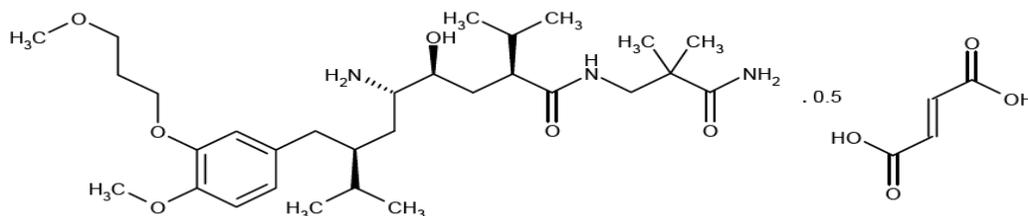
Aliskiren fumarate

Chemical Name: (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]octanamide hemifumarate.

Molecular Formula: C<sub>30</sub>H<sub>53</sub>N<sub>3</sub>O<sub>6</sub> · 0.5 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

Molecular Weight: 609.8 salt form (551.8 as a free base)

Chemistry Review Data Sheet

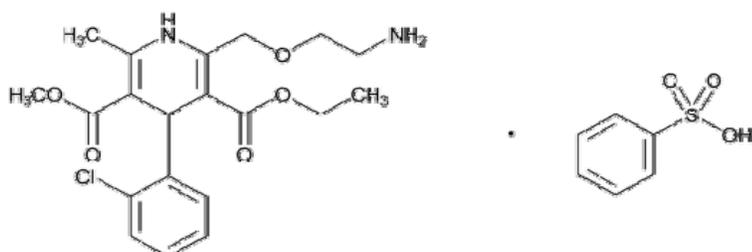


Amlodipine besylate

Chemical Name/USAN: 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate

Molecular Formula: C<sub>20</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>5</sub> · C<sub>6</sub>H<sub>6</sub>O<sub>3</sub>S

Molecular Weight: 567.05



**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Amlodipine besylate	1	Adequate	04-03-2010	Drug substance
(b) (4)	II	(b) (4)	Amlodipine besylate (b) (4)	1	Adequate	08-04-2010	Drug substance
(b) (4)	II	(b) (4)	Amlodipine besylate	3	Adequate	09-26-2008	Drug substance
(b) (4)	IV	(b) (4)	(b) (4) Film coating	4	N/A	N/A	Tablet film coating
(b) (4)	III	(b) (4)	HDPE Bottle 90 cc Squire, (b) (4)	3	Adequate	N/A	Packaging

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	HDPE Bottle 90 cc Squire, (b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	HDPE bottle 45 cc round (b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no related revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 72,407	01-FEB-2007	

18. STATUS:

Chemistry Review Data Sheet

**ONDC:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
EES	Overall evaluation "Acceptable"	04/27/2010	Office of Compliance
Pharm/Tox	Approvable	06/03/2010	Gowra Jagadeesh, Ph.D.
Biopharmaceutics ONDQA	Acceptable	06/11/2010	Tien-Mien Chen, Ph.D.
Methods Validation	Acceptable as per this Review by Dr. Soldatova		Lyudmila Soldatova, Ph.D.
DMEPA (container/carton labels)	Pending		
DMEPA	Proprietary name is conditionally acceptable	02/02/2010	Tselain Jones Smith, PharmD
EA	Adequate; FONSI is recommended	6/28/2010 6/28/2010	Emily A. McVey, Ph.D. (OPS/IO)

# The Chemistry Review for NDA 22-314

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 22-545 for Tekamlo film-coated Tablets is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint. Based on the drug product stability data including ONDQA Biopharmaceutics recommendation on dissolution specification, the shelf-life of 24-month expiration period is recommended for 150/5 mg, 150/10 mg and 300/10 mg strengths of the drug product packaged in 30 count (90 cc), 90 count and 100 count (b) (4) HDPE bottles with desiccant stored under controlled room temperature conditions, protected from heat and moisture. An 18-month expiration period is recommended for 300/5 mg strength of the drug product packaged in 30 count (90 cc), 90 count and 100 count (b) (4) HDPE bottles with desiccant stored under controlled room temperature conditions, protected from heat and moisture. An 18-month expiration period is granted for all strengths of the drug product packaged in blisters of 10 (2 x 5) stored under controlled room temperature conditions. An 18-month expiration period is granted for drug product packaged in 7 count and 14 count 45 cc, (b) (4) HDPE, round bottles with desiccant. (b) (4)

The Tekamlo tablets in 100 count (b) (4) bottles are not planned to be marketed at this time. The overall Acceptable recommendation was assigned by OC for all drug substance and drug product facilities.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

Aliskiren/Amlodipine Tablets is a fixed dose combination of two active ingredients, aliskiren hemifumarate (SPP100) and amlodipine besylate; they are developed as once daily dose tablets. Aliskiren hemifumarate is a rennin inhibitor, and amlodipine besylate is a calcium channel blocker. Both aliskiren and amlodipine are approved monotherapy products under Novartis's NDA 21-985 (Tekturna) and Pfizer's NDA 19-787 (Norvasc), respectively.

## Executive Summary Section

**Drug Product**

Aliskiren/Amlodipine film-coated tablets are immediate release dosage forms for oral administration for the treatment of hypertension. Four tablet strengths, 150 mg/5 mg, 150 mg/10 mg, 300/5 mg and 300/10 mg of aliskiren and amlodipine have been developed. The different strengths of tablets are distinguished by color, by weight and size (150/5 mg and 150/10 mg differ by weight and size from 300/5 and 300/10 tablets), and by different debossing code on one side of tablets.

Novartis has developed for marketing a (b) (4) tablet using existing commercial (b) (4) of both drugs, based on bioequivalence studies with the monotherapy forms of aliskiren and amlodipine. The 150/10 mg and 300/10 mg (b) (4) film-coated tablet formulations containing (b) (4) of crospovidone in the external phase were shown to be bioequivalent to the monotherapy forms of aliskiren and amlodipine. The 300/10 mg and 150/5 mg strengths are weight and dose proportional whereas the 150/5 mg and 150/10 mg strengths are compositionally similar, and the 300/5 mg and 300/10 mg strengths are compositionally similar as well. A biowaiver request for the 150/5 mg and 300/5 mg SPA100 film-coated tablets has been granted by ONDQA biopharm reviewer (Review by Dr. Tien-Mien Chen dated 6/11/2010). The compendial excipients are used in the tablet formulation. The coating premixes are a combination of ingredients which meet compendial or CFR requirements. The specifications to control release and stability of the drug substance include standard tests for solid oral dosage forms as well as tests for (b) (4) used in the manufacture of tablets, and test for potentially (b) (4) impurities. Specification limits for impurities were consulted with pharm/tox reviewer; based on this consultation, they are acceptable (Review dated 06/03/2010). Dissolution method and specification for drug product were consulted with ONDQA biopharm reviewer; final specification proposed by the applicant, was accepted by biopharm reviewer as follows: Apparatus: 1 (Basket); Speed: 100 rpm; Medium: 0.01N HCL (pH 2.0), 500 ml at 37°C; Specifications: Q (b) (4) at 30 min for both aliskiren and amlodipine.

The SPA100 tablets will be marketed in HDPE bottles with desiccant and child resistant closures, and in blisters (b) (4). A 30 count tablets of all strengths will be marketed in (b) (4) 90 cc HDPE bottles. A 90 count tablets of 150/5 and 150/10 strengths will be marketed in (b) (4) HDPE bottles, and 90 count tablets of 300/5 and 300/10 strengths will be marketed in (b) (4) HDPE bottles. The 100 count tablets will be not marketed at this time. All dosage strengths also will be marketed in 10 count (b) (4) blister packs with a (b) (4) (b) (4) aluminum foil. There will be also (b) (4) 7 count HDPE bottle (45 cc) and 10-count (2 x 5) blister packs [14 count HDPE bottle (45 cc) are utilized for stability studies but will not be used].

Novartis has provided two comparability protocols in an Amendment dated 19-Feb-2010: protocol for post-approval change in packaging (change in the number of units or labeled amount of unit-of-use container), and protocol for post-approval change in blister packaging components. Both comparability protocols are acceptable.

## Executive Summary Section

The 12-month stability data for pilot scale batches has been provided in the Amendment dated 25-Mar-2010 as per agreement during the pre-NDA meeting. The bracketing design of the stability protocol was proposed for the 90 count HDPE bottle (b) (4) by testing the 30 count HDPE bottle (90 cc) and the 100 count HDPE bottle (b) (4) and for the 14 count HDPE bottle (45 cc) by testing the 30 count HDPE bottle (90 cc) and the (b) (4). Stability studies provided a basis for granting different expiration dates for drug product of different strengths and packaged in different container /closure systems.

A 24-month expiration period is granted for 150/5 mg, 150/10 mg and 300/10 mg strengths of the drug product packaged in 30 count (90 cc), 90 count and 100 count HDPE bottles with desiccant stored under controlled room temperature conditions. An 18-month expiration period is granted for 300/5 mg strength of the drug product packaged in 30 count (90 cc), 90 count and 100 count HDPE bottles with desiccant stored under controlled room temperature conditions. An 18-month expiration period is granted for all strengths of the drug product packaged in 10-count blisters stored under controlled room temperature conditions. An 18-month expiration period is granted for drug product packaged in (b) (4) and 14 count 45 cc, HDPE, round bottles with desiccant.

The Overall “Acceptable” recommendation is issued on 27-Apr-2010 for all drug substance and drug product manufacturing sites.

The Environmental Assessment (EA) submitted by Novartis is acceptable; a FONSI (A Finding of No Significant Impact) is recommended on 6/28/2010.

The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) protected from heat and moisture.

### **Drug Substance**

Two drug substances are used in the formulation of SPA100 tablets: aliskiren fumarate and amlodipine besylate. Drug substance aliskiren hemifumarate is the subject of the approved NDA 21-985 held by Novartis, and all CMC information is cross-referenced to this application and all subsequent supplements. Amlodipine besylate is obtained from two sources, (b) (4). (b) (4) CMC information for this drug substance is provided in the respective DMFs. The DMF (b) (4) and DMF (b) (4) that contains a new synthetic process for (b) (4), are found to be adequate ( DMF (b) (4) is adequate with Information request). DMF (b) (4) is adequate. The analytical comparison of batches from each supplier/process demonstrated that the drug substance batches from 3 sources are equivalent.

### **B. Description of How the Drug Product is Intended to be Used**

SPA100 tablets of different strengths are supplied as following available combinations: 150 mg/5 mg, 150 mg/10 mg, 300/5 mg and 300/10 mg (aliskiren and amlodipine). All strengths are packaged in bottles of 30 and 90 count and unit dose blister packages. Three different sets of

## Executive Summary Section

packaging configurations, Commercial, Hospital and Physician sample are presented. The drug will be administered orally.

Dosage and Administration:

- Add-on therapy OR initial therapy: initiate with 150/5 mg. Titrate as needed up to a maximum of 300/10 mg
- Majority of effect attained within 1 week.
- Replacement therapy: may be substituted for titrated components.
- One tablet daily, with a routine pattern with regard to meals.
- May be administered with other antihypertensive agents.

**C. Basis for Approvability or Not-Approval Recommendation**

The applicant has addressed all deficiencies satisfactory. The applicant has accepted the dissolution specifications recommended by FDA. The amlodipine drug substance DMF is found to be Adequate with Information request. The Environmental Assessment (EA) submitted by Novartis is acceptable; a FONSI (A Finding of No Significant Impact) is recommended.

(b) (4)

**III. Administrative****A. Reviewer's Signature**

See electronic signatures in DFS.

**B. Endorsement Block**

Chemist Name: Lyudmila N. Soldatova, Ph.D.  
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.  
Chemistry Project Manager Name: Don Henry  
Clinical Project Manager Name: Michael V. Monteleone

**C. CC Block**

See DFS.

13 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

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LYUDMILA N SOLDATOVA  
08/04/2010

RAMESH K SOOD  
08/04/2010

# **NDA 22-545**

## **Aliskiren and Amlodipine Tablets**

### **Novartis Pharmaceuticals Corporation**

#### **Division of Cardiovascular and Renal products**

**Lyudmila N. Soldatova, Ph. D.**  
**DPAI/ONDQA**

**Review of Chemistry, Manufacturing, and Controls**

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# Chemistry Review Data Sheet

1. NDA 22-545
2. REVIEW #1
3. REVIEW DATE: June 2, 2010
4. REVIEWER: Lyudmila N. Soldatova
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

29-OCT-2009

Amendment

07-DEC-2009

Amendment

26-JAN-2010

Amendment

19-FEB-2010

Amendment

25-FEB-2010

Amendment

12-MAR-2010

Amendment

25-MAR-2010

Amendment

06-APR-2010

Amendment

26-APR-2010

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Address: One Health Plaza  
East Hanover, NJ 07936Representative: Lori Ann Kneafsey  
Associate Director, Drug regulatory Affairs

## Chemistry Review Data Sheet

Telephone: 862-778-5369

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Tekamlo (proposed)
- b) Non-Proprietary Name (USAN): aliskiren fumarate/amlodipine besylate
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 4
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

## 10. PHARMACOL. CATEGORY: Hypertension

## 11. DOSAGE FORM: Tablets

## 12. STRENGTH/POTENCY: 150/5 mg, 150/10 mg, 300/5 mg, and 300/10 mg,

## 13. ROUTE OF ADMINISTRATION: Oral

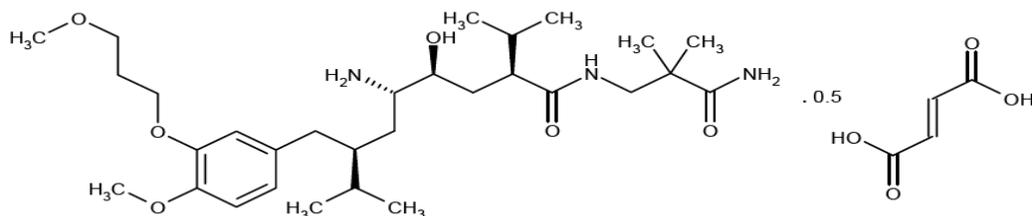
14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#) SPOTS product – Form Completed Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Aliskiren fumarateChemical Name: (2*S*,4*S*,5*S*,7*S*)-N-(2-Carbamoyl-2- methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]octanamide hemifumarate.Molecular Formula: C<sub>30</sub>H<sub>53</sub>N<sub>3</sub>O<sub>6</sub> · 0.5 C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>

Molecular Weight: 609.8 salt form (551.8 as a free base)

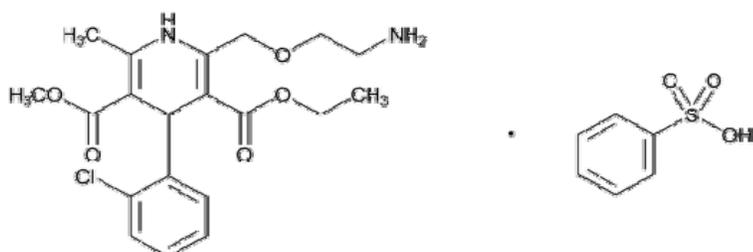
## Chemistry Review Data Sheet


Amlodipine besylate

Chemical Name/USAN: 3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate

Molecular Formula: C<sub>20</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>5</sub> · C<sub>6</sub>H<sub>6</sub>O<sub>3</sub>S

Molecular Weight: 567.05



## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Amlodipine besylate	1	Adequate	04-03-2010	Drug substance
(b) (4)	II	(b) (4)	Amlodipine besylate (b) (4)	1	Inadequate	03-03-2010	Drug substance
(b) (4)	II	(b) (4)	Amlodipine besylate	3	Adequate	09-26-2008	Drug substance
(b) (4)	IV	(b) (4)	(b) (4) Film coating	4	N/A	N/A	Tablet film coating
(b) (4)	III	(b) (4)	HDPE Bottle 90 cc Squire (b) (4)	3	Adequate	N/A	Packaging

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	HDPE Bottle 90 cc Squire, (b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	HDPE bottle 45 cc round (b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	N/A	Packaging

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no related revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 72,407	01-FEB-2007	

18. STATUS:

Chemistry Review Data Sheet

**ONDC:**

<b>CONSULTS/ CMC RELATED REVIEWS</b>	<b>RECOMMENDATION</b>	<b>DATE</b>	<b>REVIEWER</b>
EES	Overall evaluation "Acceptable"	04/27/2010	Office of Compliance
Pharm/Tox	Approvable	06/03/2010	Gowra Jagadeesh, Ph.D.
OCPB	Pending		Divya Menon-Andersen, Ph.D.
Methods Validation	Acceptable as per this Review by Dr. Soldatova		Lyudmila Soldatova, Ph.D.
DDMAC	Pending		
DMEPA	Proprietary name is conditionally acceptable	02/02/2010	Tselain Jones Smith, PharmD
EA	Pending		Raanan Bloom, Ph.D. (OPS/PARS)

# The Chemistry Review for NDA 22-314

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 22-545 for SPA100 film-coated Tablets cannot be approved in its current form from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug product deficiencies indicated in the IR Letter dated 28-May-2010, upon resolution of the deficiencies in amlodipine drug substance DMF (b) (4) (Deficiency Letter dated 10-Mar-2010), and on the Evaluation of the Environmental Assessment.

Additional review addendum will be written once these issues have resolved.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Aliskiren/Amlodipine Tablets is a fixed dose combination of two active ingredients, aliskiren hemifumarate (SPP100) and amlodipine besylate; they are developed as once daily dose tablets. Aliskiren hemifumarate is a rennin inhibitor, and amlodipine besylate is a calcium channel blocker. Both aliskiren and amlodipine are approved monotherapy products under Novartis's NDA 21-985 (Tekturma) and Pfizer's NDA 19-787 (Norvasc), respectively.

#### Drug Product

Aliskiren/Amlodipine film-coated tablets are immediate release dosage forms for oral administration for the treatment of hypertension. Four tablet strengths, 150 mg/5 mg, 150 mg/10 mg, 300/5 mg and 300/10 mg of aliskiren and amlodipine have been developed. The different strengths of tablets are distinguished by color, by weight and size (150/5 mg and 150/10 mg differ by weight and size from 300/5 and 300/10 tablets), and by different debossing code on one side of tablets.

Novartis has developed for marketing a (b) (4) tablet using existing commercial (b) (4) of both drugs, based on bioequivalence studies with the monotherapy forms of aliskiren and amlodipine. The 150/10 mg and 300/10 mg (b) (4) film-coated tablet formulations containing (b) (4) of crospovidone in the external phase were shown to be bioequivalent to the

## Executive Summary Section

monotherapy forms of aliskiren and amlodipine. The 300/10 mg and 150/5 mg strengths are weight and dose proportional whereas the 150/5 mg and 150/10 mg strengths are compositionally similar, and the 300/5 mg and 300/10 mg strengths are compositionally similar as well. A biowaiver request for the 150/5 mg and 300/5 mg SPA100 film-coated tablets has been submitted based on compositional proportionality (300/10 – 150/5 mg) and compositional similarity (300/10 – 300/5 mg). The acceptability of this request is being evaluated by ONDQA biopharm reviewer.

The compendial excipients are used in the tablet formulation. The coating premixes are a combination of ingredients which meet compendial or CFR requirements. The specifications to control release and stability of the drug substance include standard tests for solid oral dosage forms as well as tests for (b) (4) used in the manufacture of tablets, and test for potentially (b) (4) impurities. Specification limits for impurities were consulted with pharm/tox reviewer; based on this consultation, they are acceptable. Dissolution method and specification for drug product was consulted with ONDQA biopharm reviewer; final specification proposed by the applicant, was accepted by biopharm reviewer.

The SPA100 tablets will be marketed in HDPE bottles with desiccant and child resistant closures, and in blisters (b) (4). A 30 count tablets of all strengths will be marketed in (b) (4) 90 cc HDPE bottles. A 90 count tablets of 150/5 and 150/10 strengths will be marketed in (b) (4) HDPE bottles, and 90 count tablets of 300/5 and 300/10 strengths will be marketed in (b) (4) HDPE bottles. The 100 count tablets will be not marketed at this time. All dosage strengths also will be marketed in (b) (4) blister packs with a (b) (4) (b) (4) aluminum foil. There will be also (b) (4) 7 count HDPE bottle (45 cc) [14 count HDPE bottle (45 cc) are utilized for stability studies but will not be used].

Novartis has provided two comparability protocols an Amendment dated 19-Feb-2010: protocol for post-approval change in packaging (change in the number of units or labeled amount of unit-of-use container), and protocol for post-approval change in blister packaging components.

The 12-month stability data for pilot scale batches has been provided in the Amendment dated 25-Mar-2010 as per agreement during the pre-NDA meeting. The bracketing design of the stability protocol was proposed for the 90 count HDPE bottle (b) (4) by testing the 30 count HDPE bottle (90 cc) and the 100 count HDPE bottle (b) (4), and for the 14 count HDPE bottle (45 cc) by testing the 30 count HDPE bottle (90 cc) and the 7 count HDPE bottle (45 cc). Stability studies provided a basis for granting different expiration dates for drug product of different strengths and packaged in different container /closure systems.

A 24-month expiration period is granted for 150/5 mg, 150/10 mg and 300/10 mg strengths of the drug product packaged in 30 count (90 cc), 90 count and 100 count HDPE bottles with desiccant stored under controlled room temperature conditions. An 18-month expiration period is granted for 300/5 mg strength of the drug product packaged in 30 count (90 cc), 90 count and 100 count HDPE bottles with desiccant stored under controlled room temperature conditions. An 18-month expiration period is granted for all strengths of the drug product packaged in blisters stored under controlled room temperature conditions. An 18-month expiration period is

## Executive Summary Section

granted for drug product packaged in 7 count and 14 count 45 cc, HDPE, round bottles with desiccant.

The Overall "Acceptable" recommendation is issued on 27-Apr-2010 for all manufacturing sites; the summary report is attached (see Attachment for this Review).

Evaluation of the Environmental Assessment is pending; it is consulted with OPS/PARS.

The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) protected from heat and moisture.

### **Drug Substance**

Two drug substances are used in the formulation of SPA100 tablets: aliskiren fumarate and amlodipine besylate. Drug substance aliskiren hemifumarate is the subject of the approved NDA 21-985 held by Novartis, and all CMC information is cross-referenced to this application and all subsequent supplements. Amlodipine besylate is obtained from (b) (4). CMC information for this drug substance is provided in the respective DMFs. The DMF (b) (4) is adequate while DMF (b) (4) that contains a new synthetic process for amlodipine, is currently inadequate (deficiency letter dated 10-Mar-2010 was sent to DMF holder). DMF (b) (4) is adequate. The analytical comparison of batches from each supplier/process demonstrated that the drug substance batches from 3 sources are equivalent.

### **B. Description of How the Drug Product is Intended to be Used**

SPA100 tablets of different strengths are supplied as following available combinations: 150 mg/5 mg, 150 mg/10 mg, 300/5 mg and 300/10 mg (aliskiren and amlodipine). All strengths are packaged in bottles of 30 and 90 count and unit dose blister packages. Three different sets of packaging configurations, Commercial, Hospital and Physician sample are presented. The drug will be administered orally.

#### **Dosage and Administration:**

- Add-on therapy OR initial therapy: initiate with 150/5 mg. Titrate as needed up to a maximum of 300/10 mg
- Majority of effect attained within 1 week.
- Replacement therapy: may be substituted for titrated components.
- One tablet daily, with a routine pattern with regard to meals.
- May be administered with other antihypertensive agents.

### **C. Basis for Approvability or Not-Approval Recommendation**

**Executive Summary Section**

NDA 22-545 for SPA100 Tablets cannot be approved in its current form from the CMC standpoint. Approvability will be based on the Novartis's response to FDA comments sent in IR Letter dated 28-May-2010 (comments are listed in the section "List of Deficiencies", p. 116 of this Review), resolution of the deficiencies in amlodipine drug substance DMF (b) (4), and on the acceptable evaluation of the Environmental Assessment.

**III. Administrative****A. Reviewer's Signature**

See electronic signatures in DFS.

**B. Endorsement Block**

Chemist Name: Lyudmila N. Soldatova, Ph.D.  
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.  
Chemistry Project Manager Name: Don Henry  
Clinical Project Manager Name: Michael V. Monteleone

**C. CC Block**

See DFS.

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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/

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LYUDMILA N SOLDATOVA  
06/09/2010

RAMESH K SOOD  
06/09/2010

## Initial Quality Assessment Branch I

<b>OND Division:</b>	Division of Cardiovascular and Renal Products
<b>NDA:</b>	22-545
<b>Applicant:</b>	Novartis
<b>Letter Date:</b>	29 Oct 2009
<b>Stamp Date:</b>	29 Oct 2009
<b>PDUFA Date:</b>	29 Aug 2009
<b>Tradename:</b>	Tekamlo (proposed)
<b>Established Name:</b>	Aliskiren and amlodipine
<b>Dosage Form:</b>	Tablets, 150/5 mg, 150/10 mg, 300/5 mg and 300 /10mg
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Hypertension
<b>Assessed by:</b>	Kasturi Srinivasachar
<b>ONDQA Fileability:</b>	Yes

### Summary

This is an e-CTD submission for a fixed dose combination drug product of aliskiren hemifumarate, a direct renin inhibitor and amlodipine besylate, a calcium channel blocker. Both aliskiren and amlodipine are approved monotherapy products under Novartis' NDA 21-985 (Tekturna) and Pfizer's NDA 19-787(Norvasc). Clinical trials for this combination drug product were carried out under INDs 62,976 (aliskiren monotherapy) and 72,407 (alsikiren/amlodipine fixed dose combination). The pivotal clinical efficacy trials used the final market image fixed dose combination tablets, whereas the long term safety trial employed the free combination of aliskiren and amlodipine. Bioequivalence studies were carried out with the 150/10 mg and 300/10 mg strengths and the two individual monotherapy products in free combination, to allow bridging to existing efficacy and safety data for the monotherapies. There have been no CMC specific meetings with Novartis in connection with this NDA. A multi-disciplinary pre-NDA meeting was scheduled for Dec. 17, 2008 but was cancelled by the sponsor based on the Agency's preliminary responses. The main CMC question asked by the sponsor concerned the acceptability of their bracketing proposal for their registration stability protocol. This involved bracketing the 90 count HDPE bottles by testing the 30 and 100 count bottles. A bracketing design for physician sample bottles was also proposed. The proposals were considered acceptable. Novartis was also interested in feedback on their dissolution method, specifically, if a (b) (4) would be acceptable. They were told to provide a complete dissolution method development report for review before a definitive response could be provided. A (b) (4) would be acceptable, if adequately justified.

### Drug Substance

Aliskiren hemifumarate was developed by Novartis and all CMC information for this drug substance is by cross-reference to NDA 21-985 and its supplements. Two other combination drug products using this drug substance have been approved – Tekturna HCT (aliskiren/hydrochlorothiazide), NDA 22-107 and Valturna (aliskiren/valsartan), NDA 22-217. Aliskiren hemifumarate is highly water soluble but has low permeability – BCS class 3.

Amlodipine besylate is obtained from two sources, (b) (4) (b) (4). CMC information for this drug substance is provided through DMFs – DMF (b) (4) and DMF (b) (4). DMF (b) (4) was last reviewed on Aug 6, 2008 and found adequate; DMF (b) (4) also held by (b) (4) is for a new process and has not been reviewed. DMF (b) (4) was last reviewed on Sep 26, 2008 and deemed adequate. It is stated that an analytical comparison of amlodipine besylate manufactured by (b) (4) establishes the equivalence of drug substance batches from both suppliers. There is an USP monograph for amlodipine besylate.

### Drug Product

Four strengths, 150 mg/5 mg, 150 mg/10 mg, 300/5 mg and 300/10 mg of aliskiren and amlodipine have been developed for commercialization as immediate release film coated tablets. The different strengths are distinguished by color and debossing code. Standard compendial excipients are used in the formulation. The premixes used for film coating are composed of compendial ingredients or colors that meet 21CFR.

Based on bioequivalence studies with the free forms of aliskiren and amlodipine, a (b) (4) tablet using existing commercial (b) (4) of both drugs was developed for marketing. 150/10 mg and 300/10 mg (b) (4) film-coated tablet formulations containing (b) (4) of crospovidone in the external phase were shown to be bioequivalent to the free forms of aliskiren and amlodipine. The 300/10 mg and 150/5 mg strengths are weight and dose proportional whereas the 150/5 mg and 150/10 mg strengths are compositionally similar with differences only in the amount of microcrystalline cellulose to account for the different amounts of amlodipine besylate. Similarly, the 300/5 mg and 300/10 mg strengths are compositionally similar.

The manufacturing process consists of (b) (4)

Standard specifications for tablets have been proposed and include tests for the (b) (4) (b) (4) used in product manufacturing as well as potentially (b) (4) impurities. The product will be marketed in HDPE bottles with desiccant and (b) (4) blisters. Stability data have been provided for up to 6 months for pilot scale (b) (4) (b) (4) tablets) batches. Data for an additional 6 months are expected during the review cycle.

### Critical Review Issues

#### Drug Substance

- (b) (4) for amlodipine besylate is stated to be for a new process which needs a detailed evaluation since it has never been reviewed.
- Have the physical properties and impurity profiles of amlodipine besylate from both (b) (4) processes been shown to be equivalent to each other and to the (b) (4) substance?

## Drug Product.

- [REDACTED] (b) (4)  
[REDACTED] Have details of these tests been provided and are they sufficient to justify the lack of routine in-process tests for this attribute?
- The ONDQA Biopharmaceutics team should be consulted for the dissolution method development and acceptance criteria. The biowaiver request for the 150/5 mg and 300/5 mg strengths and the in vitro dissolution data supporting the use of EU sourced amlodipine tablets versus US manufactured amlodipine tablets should also be brought to their attention.
- Is the proposed limit of NMT (b) (4) ppm for the total of [REDACTED] (b) (4) [REDACTED] acceptable for these potential genotoxins? Novartis is proposing a limit test which presumably means that the results will be presented as “meets” or [REDACTED] (b) (4) rather than actual values. Is this acceptable?
- Impurity [REDACTED] (b) (4) has been specified with a release and shelf-life limit of NMT [REDACTED] (b) (4). Is this a new aliskiren degradant since it was not specified in the monotherapy NDA or in the combination product with valsartan. Has it been qualified at the specified level?
- Degradation product [REDACTED] (b) (4) is claimed to be formed by [REDACTED] (b) (4) addition of the amino group of amlodipine to the fumaric acid component of aliskiren. The limits have been set at NMT [REDACTED] (b) (4) for release and shelf life and it is stated that the latter acceptance criterion has been established through previous stability studies and has been toxicologically qualified. This should be confirmed with the pharmacology/toxicology reviewer. It is not clear which stability studies support this limit. This degradation product seems to be highly temperature/humidity sensitive since its levels under accelerated storage conditions are markedly higher than at room temperature.
- It is noted that there are stability failures at 40°C/75%RH for the 300/5 mg strength stored in trade HDPE bottles and for all strengths in blisters under these accelerated conditions. The expiration dating period granted should take this into account.

## Labeling

- Updated container labels should be requested after the tradename is approved. The package insert has the incorrect established name, [REDACTED] (b) (4). This should be changed to “amlodipine”.

## Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities have been entered into EES and the reviewer should verify the accuracy and completeness of the entries. A single CMC reviewer is recommended.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead  
Ramesh Sood, Ph.D.  
Branch Chief

Nov 18, 2009  
Date  
Nov 18, 2009  
Date

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/

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KASTURI SRINIVASACHAR  
11/18/2009

RAMESH K SOOD  
11/18/2009

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

**NDA Number: 22-545**

**Supplement Number and Type:  
Original NDA**

**Established/Proper Name:**

**Aliskiren and Amlodipine  
Tablets**

**Applicant: Novartis  
Pharmaceuticals  
Corporation**

**Letter Date: 29-Oct-2009**

**Stamp Date: 29-Oct-2009**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		Confusion in the Title of Section 3.2.P.4
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		OC recommendation is Acceptable for all facilities except for one (inspection is assigned for drug substance manufacturer)
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>	N/A		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?			EA report is provided; consult is requested

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	X		Drug substance aliskiren hemifumarate is cross-referenced to NDA 21-985 and its supplements. Drug substance amlodipine besylate is referenced to DMF (b) (4) and DMF (b) (4) (b) (4) and (b) (4).
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Refer to Item 12.
14.	Does the section contain information regarding the characterization of the DS?			Refer to Item 12.
15.	Does the section contain controls for the DS?			Refer to Item 12. Specification and batch analyses for amlodipine besylate are provided in NDA submission.
16.	Has stability data and analysis been provided for the drug substance?			Refer to Item 12.
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		Biowaiver is requested for the 150/5 mg and 300/5 mg strengths
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		The 6-month stability data is provided; additional stability data will be provided during the review cycle according to pre-NDA agreement.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>F. METHODS VALIDATION (MV)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
29.	Is there a methods validation package?	X		

<b>G. MICROBIOLOGY</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	N/A

<b>H. MASTER FILES (DMF/MAF)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Drug substance DMF (b) (4) and DMF (b) (4) have been reviewed and were found adequate. DMF (b) (4) is for a new process for amlodipine besylate, and has not been reviewed; information is complete. The information for DMFs for packaging components is complete. LoAs for all referenced DMFs are provided.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	Type II	(b) (4)	Amlodipine Besylate	10-Jul-2009	
(b) (4)	Type II	(b) (4)	Amlodipine Besylate	15-Jul-2009	
(b) (4)	Type II	(U) (4)	Amlodipine Besylate	06-Aug-2009	

<b>I. LABELING</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		“Run” text is provided for container labels, not draft labels

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA or Supplement (ONDQA)**

<b>J. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		X	Describe potential review issues here or on additional sheets

*{See appended electronic signature page}*

*12/18/2009*

Kasturi Srinivasachar/Lyudmila Soldatova  
Division of Pre-Marketing Assessment #1  
Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

*12/08/2009*

Ramesh Sood  
Division of Pre-Marketing Assessment #1  
Office of New Drug Quality Assessment

Date

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/

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LYUDMILA N SOLDATOVA  
12/08/2009

RAMESH K SOOD  
12/08/2009