CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-990

CHEMISTRY REVIEW(S)

Chemistry Review Data Sheet

1. NDA 21-990

2. REVIEW #: 2

3. REVIEW DATE: 6-19-2007

4. REVIEWER: Haripada Sarker, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original (N-000)	February 22, 2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (N-000)BC - Dissolution	February 12, 2007
Amendment (N-000)BC - Dissolution	May 11, 2007
Amendment (N-000)BC – Mfg. change	March 2, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceutical Corporation
Address:	One Health Plaza East Hanover, NJ 07936
Representative:	Donna Vivelo
Telephone:	862-778-3572

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Exforge®
b) Non-Proprietary Name: Amlodipine besylate and Valsartan
c) Code Name/#: VAA489A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 4
- Submission Priority: S

e) Proposed Trade Name: Exforge®

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Hypertension.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5/160mg; 10/160mg; 5/320mg; 10/320mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

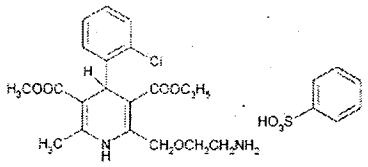
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

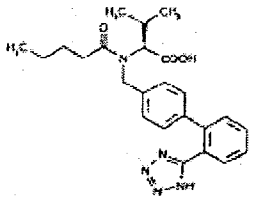
__X__Not a SPOTS product

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

Structure:



Amlodipine besylate



Valsartan

Name (drug substance)	Amlodipine besylate	Valsartan
Chemical Name (USAN)	Amlodipine besylate	Valsartan

17. RELATED/SUPPORTING DOCUMENTS: N/A

The Chemistry Review for NDA 21-990

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for APPROVAL from a chemistry, manufacturing and controls standpoint. Based on drug product updated stability data on dissolution as recommended by Agency in review cycle #1, following DP shelf-lives are granted. Since there is one point dissolution test data is available for all the strengths using new test method, and no bridging study is available between old and new dissolution method and specification, a conservative approach is taken in assigning the following shelf-lives. DP strengths, ——— thus no shelf-lives are granted for these strengths.

160/5 mg, 160/10 mg, and 320/5 mg strengths:
18 months: 2 count HDPE bottles, ——— blister packs.
18 months: ——— 30 count, 90 count and 100 count HDPE bottles.
320/10 mg strength:
12 months: ——— count ———
18 months: ——— 30 count, 90 count and 100 count ———

In a separate amendment, applicant has proposed some changes in manufacturing of ——— ———. These changes were found to be adequate.

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

N/A

II. Summary of Chemistry Assessments

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

Exforge® (Amlodipine besylate and Valsartan) is formulated as combination tablets and is supplied in ——— 5/160mg; 10/160mg; 5/320mg; 10/320m (Amlodipine/Valsartan) strengths. However, the current plan excludes the marketing of ——— Amlodipine besylate is expressed as free-base for its strength in combination product. Active ingredients include Amlodipine besylate and Valsartan. Inactive ingredients consist of microcrystalline cellulose, crospovidone, magnesium stearate, colloidal silicon dioxide, iron oxide and coating premix. Two different formulations, monolayer and bi-layer are developed for tablets manufacturing. The strengths, ——— 5/160mg; 10/160mg are formulated as monolayer film-coated tablets, based on the commercial Diovan (valsartan). However, for strengths, 5/320mg; 10/320mg the Valsartan component of fixed combination was not bioequivalent to the free combination. The extent of absorption of Valsartan was about 17%

and 10%, respectively, less than that from the free combination. To achieve bioequivalence with respect to both Valsartan and Amlodipine, 5/320mg; 10/320mg film-coated tablets were developed using a bi-layer tablet approach. In bi-layer tablets, the active ingredients are more discrete, and ——— of Valsartan and Amlodipine besylate ——— together into tablets.

The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]. Depending on storage conditions and formulations, four different shelf-lives are proposed (12 months ——— for the drug product. The drug product stability data are found to be acceptable except dissolution method and specification in NDA review cycle #1. Agency recommended revised specification and method for DP dissolution, which was later agreed by the company. In the current submission, Novartis provided dissolution test data ca. 18 months on registration stability samples using the dissolution method proposed by FDA. However, no additional chemical test data on stability are provided that corresponds to latest dissolution time-points. Based on the dissolution test data provided for the DP as well as the stability data provided in NDA review cycle #1, revised DP shelf-lives are granted for DP as above (see Recommendation and Conclusion on Approvability). In should be noted that in absence of dissolution test data using revised method and specification, 12 months shelf-lives were granted in review cycle #1 for DP of all strengths and packaging conditions.

The chemical name for Amlodipine besylate is 3,5-pyridiendicarboxylic acid, 2-[(2-aminoethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3-ethyl-5-methyl ester, (±)-, monobenzenesulphonate and Valsartan is L-valine, N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-. Amlodipine besylate has Ph. Eur monograph. Both Amlodipine besylate and Valsartan were previously utilized for number of approved drugs in single or in combination products. Novartis currently purchases Amlodipine besylate from two drug substance suppliers: ——— In support of the chemistry, manufacturing and controls of Amlodipine besylate, both suppliers have separate DMFs, ——— No new controls or retest periods are proposed for Amlodipine besylate drug substances. In a recent amendment, applicant proposed some modification in manufacturing of DS, which is supplied by ——— The changes in ——— are found to be adequate.

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

Exforge® tablets of different strengths are supplied as following available combinations: ——— mg, 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg. All strengths are packaged in bottles of 30, 90 and 100 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.

In clinical trials with Exforge® (amlodipine besylate and valsartan) using amlodipine doses of 5 mg-10 mg and valsartan doses of 80 mg-320 mg, the antihypertensive effects are proposed to be increased with increasing doses.

C. Basis for Approvability Recommendation

In CMC review cycle #1, new DP dissolution method and specification was agreed after several communications. Applicant has generated dissolution test data of one latest time-point as per Agency's recommendation in review cycle #1. Applicant has validated the proposed dissolution method. Based on dissolution test data provided and the stability test data provided in review cycle #1, we granted new shelf-lives for DP as above (see Recommendation and Conclusion on Approvability).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryBranchChief/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Quynh Nguyen

C. CC Block

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___ § 552(b)(4) Draft Labeling

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/s/

Haripada Sarker
6/19/2007 10:52:04 AM
CHEMIST

Ramesh Sood
6/19/2007 11:33:36 AM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	21-990
Applicant:	Novartis
Letter Date:	23 February 2006
Stamp Date:	23 February 2006
PDUFA Date:	22 December 2006
Tradename:	Exforge
Established Name:	amlodipine besylate and valsartan
Dosage Form:	Tablets -- ———————, 5/160 mg, 10/160 mg, 5/320 mg and 10/320 mg
Route of Administration:	Oral
Indication:	Treatment of essential hypertension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes
Comments for 74-Day Letter:	No

Summary

This Application is for a fixed dose combination product consisting of two drug substances, amlodipine besylate and valsartan. Amlodipine besylate is a calcium channel blocker marketed as monotherapy by Pfizer under the tradename Norvasc. Valsartan is an angiotensin II receptor antagonist marketed as Diovan by Novartis. ———————however, their current plans exclude the marketing of the ——————→ A bracketing and matrixing strategy for drug product stability studies was proposed in an amendment to IND 65,174 and accepted with minor modifications as reflected in the minutes of the meeting held with the applicant on April, 14, 2005. This application is being filed based on phase III clinical efficacy/safety and bioequivalence studies. The clinical studies were conducted with valsartan and amlodipine besylate administered as capsules in free combination. Bioequivalence studies were then undertaken with the strengths, 2.5/80, 10/160 and 5/320 mg, ———————————————————— Biowaivers are being requested for the other 3 strengths based on compositional proportionality and similarity of in-vitro dissolution properties.

Drug Substance

Valsartan is very slightly soluble in water and in acidic media (0.1g/L in 0.1N HCl) but freely soluble at neutral or alkaline pH (> 100g/L in 0.1N NaOH). It is a L-valine derivative with one stereogenic center and is synthesized as a single enantiomer. All cmc information regarding this drug substance is by reference to the Applicant's approved NDA 20-665 (Diovan capsules) and subsequent supplements. Novartis also has other NDAs 21-283 (Diovan Tablets) and 20-818 (Diovan HCT Tablets) which utilize the same drug substance.

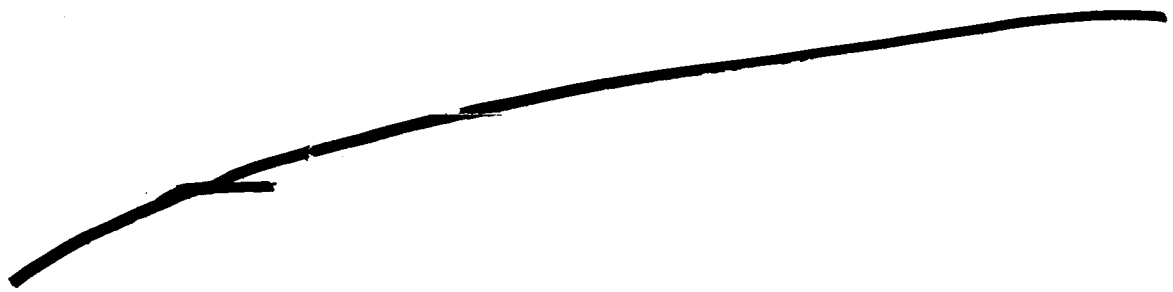
Novartis will obtain the second drug substance, amlodipine besylate, which is a white to almost white powder with slight water solubility, from 2 suppliers— ————————————

[redacted] These manufacturers have [redacted] respectively) and LOAs are provided. [redacted] has been reviewed by OGD – the initial review dated Mar. 18, 2004 concluded that the DMF was inadequate to support a generic application for amlodipine tablets and a list of deficiencies was sent to the DMF holder concerning starting materials, in-process controls, manufacturing process and specifications. The DMF holder responded to these deficiencies and OGD has determined that the DMF is now adequate (Review #2 dated June 13, 2005). [redacted] is currently unavailable since it has been checked out to an OGD reviewer. According to the OGD reviewer, Lucia Tang, the DMF is considered adequate but this needs to be verified since the review cannot be found. Amlodipine besylate does not have an USP monograph but is in the European Pharmacopoeia and both suppliers meet the requirements of the latter.

Novartis performs acceptance testing on in-coming amlodipine besylate from both suppliers and has established their own specifications. These include tests which are in addition to the Ph. Eur monograph requirements ([redacted] It is stated that based on multiple batch analysis from both suppliers that the drug substance from either [redacted] meet both Ph. Eur and Novartis' specifications.

Drug Product

All inactives used in drug product manufacture are standard [redacted] are proposed for marketing [redacted] as immediate release film coated tablets. The film coating is non-functional and is used to provide a distinctive tablet color to aid in the identification of various strengths. Based on the results of bioequivalence studies, [redacted] of the strengths are manufactured using a monolayer process whereas a bilayer process has been developed for the 5/320 mg and 10/320 mg strengths. The monolayer process was based on the commercial Diovan and Diovan HCT film coated tablets processes which the Applicant has long



The drug product is intended to be marketed in HDPE bottles with aluminum seal and child-resistant screw caps as well as [redacted] blister packs backed with a heat sealable lacquered aluminum foil.

Critical Issues for Review

Drug Substance

- Since there are 2 suppliers of amlodipine besylate, it is important to compare impurity profiles and physical properties of this drug substance from both [redacted] confirm equivalence. In addition, it should be verified whether representative drug

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/s/

Kasturi Srinivasachar
4/5/2006 11:04:46 AM
CHEMIST

Ramesh Sood
4/5/2006 12:34:22 PM
CHEMIST

NDA 21-990

Exforge®

(Amlodipine and Valsartan) Tablets

Novartis Pharmaceutical Corporation

Haripada Sarker, Ph.D.
ONDQA, DPA I

Reviewed for DCRP (HFD-110)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-990

2. REVIEW #: 1

3. REVIEW DATE: 12-8-2006

4. REVIEWER: Haripada Sarker, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 65,174	July 11, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (N-000)	February 22, 2006
Amendment (N-000)BC	August 4, 2006
Amendment (N-000)BL	August 15, 2006
Amendment (N-000)BL – Labeling	December 5, 2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceutical Corporation
Address:	One Health Plaza East Hanover, NJ 07936
Representative:	Donna Vivelo
Telephone:	862-778-3572

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Exforge®
b) Non-Proprietary Name: Amlodipine besylate and Valsartan
c) Code Name/#: VAA489A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 4
- Submission Priority: S

e) Proposed Trade Name: Exforge®

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Hypertension.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 5/160mg; 10/160mg; 5/320mg; 10/320mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

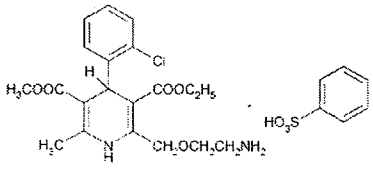
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

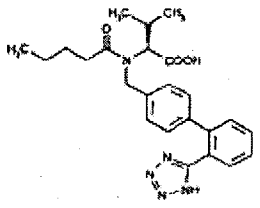
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

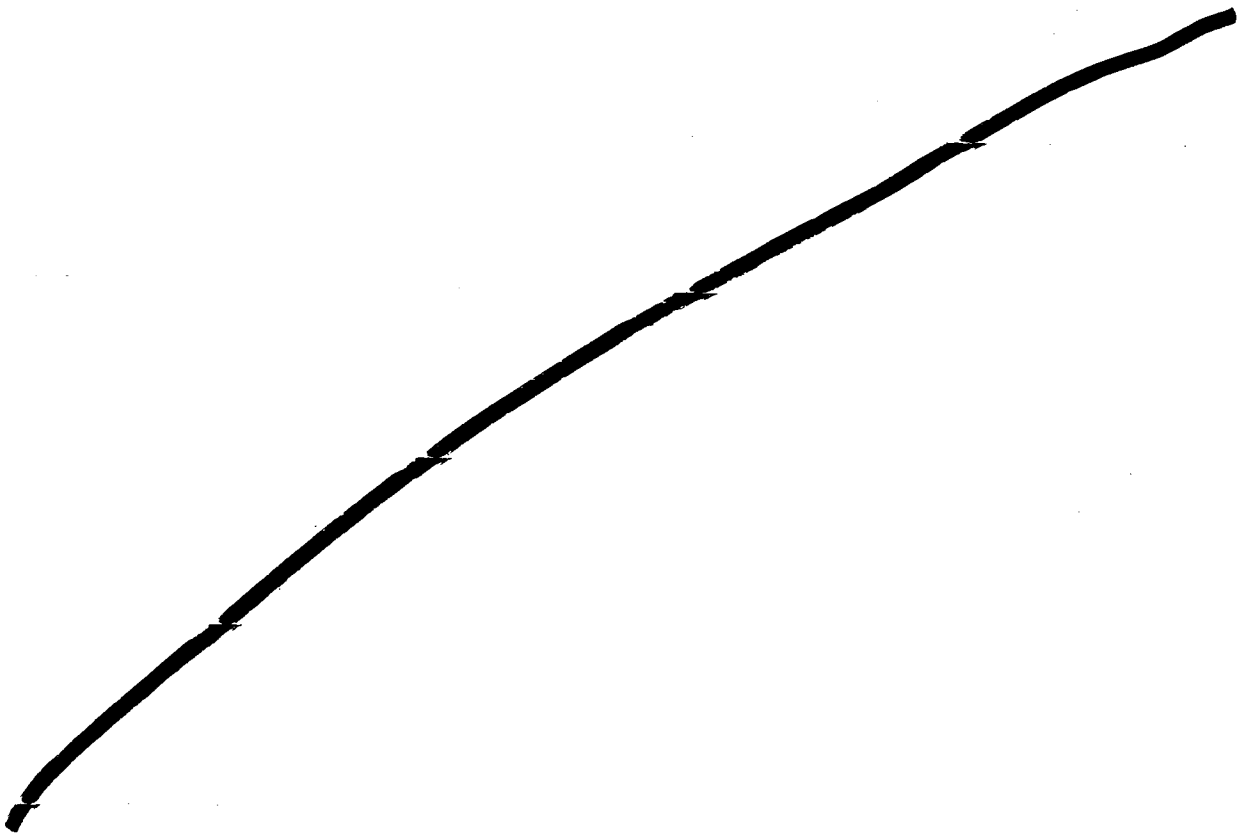
Structure:





	Amlodipine besylate	Valsartan
Name (drug substance)	Amlodipine besylate	Valsartan
Chemical Name (USAN)	Amlodipine besylate	Valsartan
Chemical Name	3,5-pyridiendicarboxylic acid, 2-[(2-aminoethoxy)methyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3-ethyl-5-methyl ester, (±)-, monobenzenesulphonate	L-valine, N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-
CAS number	1114790-99-6 (besylate salt form) 88150-42-9 (free base form)	137862-53-4
Molecular Weight	567.06	435.52
Molecular Formula	$C_{26}H_{31}ClNO_8S$. $C_6H_5SO_3H$	$C_{24}H_{29}N_5O_3$
Structural formula	As above	As above

17. RELATED/SUPPORTING DOCUMENTS:



[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents: None

18. STATUS:

ONDQA: To be filled later

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	30-November-06	J. D. Ambrogio
Biopharm	Acceptable with post-marketing commitment	1-November-06	Elena Mishina
DMETS/~~DDMAC~~	Recommended several comments	15-November-06	Kristina Arnwine (HFD-420)
Methods Validation	N/A		N/A
EA (Categorical Exclusion)	acceptable	11-September-06	Haripada Sarker
Microbiology	N/A		N/A

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/s/

Haripada Sarker
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