

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-314

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-314
From: Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date: 17-Apr-2009
Drug: Exforge HCT(amlodipine/valsartan/hydrochlorothiazide) Tablets
Route of administration: Oral
Strength: 5/160/12.5 mg, 10/160/12.5 mg/5/160/25 mg, 10/160/25 mg and 10/320/25 mg
Subject: "Approval" recommendation for NDA 22-314

Introduction: This product being developed by Novartis is for a fixed dose combination of 3 drugs, amlodipine, valsartan and hydrochlorothiazide. Valsartan was originally developed by Novartis and marketed under the tradename Diovan (NDA 20-665). Novartis later developed the combination products, Diovan HCT (valsartan/hydrochlorothiazide, NDA 20-818) and Exforge (amlodipine/valsartan, NDA 21-990).

Drug Substance: Three drug substances are used in the formulation of Exforge HCT—amlodipine besylate, valsartan and hydrochlorothiazide. CMC information for valsartan is contained in Novartis' NDA for Diovan capsules (20-665) and subsequent supplements. Amlodipine besylate is obtained from three suppliers, _____, and DMFs for each are referenced for CMC information. Amlodipine besylate from _____ were used in NDA 21-990 but _____ is a new supplier for this NDA. All three DMFs for amlodipine besylate have been found to be adequate to support this NDA. The analytical comparison of batches from each supplier demonstrated that the drug substance batches from 3 sources are equivalent. b(4)

Two suppliers of hydrochlorothiazide listed in the NDA are _____ and _____. The analytical comparison of hydrochlorothiazide batches from these two suppliers demonstrated that sourced materials are equivalent. These two DMFs have been found to be adequate to support this NDA. The drug substance obtained from these suppliers is _____ by Novartis. The CMC information for this step is provided in the NDA and was found to be satisfactory. b(4) b(4)

Drug product: Exforge HCT film-coated tablets are immediate release tablets for oral administration. Exforge HCT Tablets is a fixed dose combination of three active ingredients, amlodipine, valsartan and hydrochlorothiazide. The label claim of amlodipine is expressed as free base. A total of five strengths of Exforge tablets, i.e., 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg (amlodipine/valsartan/ hydrochlorothiazide) are manufactured. The _____ film coating provides a distinctive tablet color for the different strengths. The inactive ingredients used include microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, macrogol 4000 and talc. Additionally, individual tablets contain titanium dioxide and/or yellow and red iron oxides. The coating pre-mixes are a combination of ingredients which meet compendial or CFR requirements. All other inactive ingredients used are USP/NF. The formulations for these strengths are somewhat different from each other. The 5/160/12.5 mg and 10/160/12.5 mg b(4)

strengths are compositionally similar with variation in the amount of _____
to keep the total tablet core weight at _____. Similarly, the 5/160/25 mg and 10/160/25 mg
strengths are compositionally similar. The fifth strength, 10/320/25 is weight and dose
proportional to the 5/160/12.5 mg strength with the same _____ being used for both.

b(4)

The product is manufactured by _____

_____ The product will be marketed in _____ bottles v _____

b(4)

The quality of the drug product is ensured through appropriate in-process controls and final
product specification. The final product specification includes test and acceptance criteria for
appearance, identification (TLC and HPLC), dissolution, water content, degradation products
(HPLC), microbial limits, uniformity of dosage units by content uniformity and assay. The
proposed limits for each test were found to be acceptable. _____

b(4)

A 24-month expiration period is being assigned to the drug product packaged in 30 count, 90
count and 100 count _____ bottles when stored under controlled room temperature conditions as
requested by the applicant. A 12-month expiration period is also being assigned to the drug
product packaged in _____ blisters. _____

b(4)

The Office of Compliance has provided an overall "acceptable" recommendation for the
manufacturing sites on April 7, 2009.

Recommendation: The application is recommended for "Approval" from CMC perspective.
However, the following comments should be included in the action letter.

1. A 24-month expiration period is granted for all strengths of the drug product packaged in
30 count (90 cc), 90 count and 100 count (175 cc) _____ bottles. A 12-month expiration
period is granted for all strengths of the drug product packaged in blisters.
2. _____
3. The carton and bottle labels for the Exforge HCT tablets in 100 count _____ bottles
should be submitted as a labeling supplement before marketing them.
4. We acknowledge your commitment to update and submit the final agreed upon drug
product specification documents in the first annual report. Include "non-scored" in the
drug product description in the specification to be consistent with drug product
description in sections 3 and 16 of the package insert.

b(4)

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

/s/

Ramesh Sood
4/20/2009 03:37:48 PM
CHEMIST



CHEMISTRY REVIEW



NDA 22-314

EXFORGE HCT

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 22-314
2. REVIEW #2
3. REVIEW DATE: April 16, 2009
4. REVIEWER: Lyudmila N Soldatova
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	28-JUN-2008
Amendment	12-AUG-2008
Amendment	25-AUG-2008
Amendment	18-SEP-2008
Amendment	15-OCT-2008
Amendment	21-OCT-2008
Amendment	21-NOV-2008
Amendment	22-DEC-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	03-MAR-2009
Amendment	06-MAR-2009
Amendment	30-MAR-2009
Amendment	13-APR-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
East Hanover, NJ 07936



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Nancy A. Price
Executive Director, Drug regulatory Affairs
Telephone: 862-778-3591

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Exforge HCT
- b) Non-Proprietary Name (USAN): amlodipine/valsartan/hydrochlorothiazide
- 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: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg,
10/160/25 mg, 10/320/25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

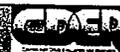
SPOTS product – Form Completed

Not a SPOTS product

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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

		Film coating				
III			3	Adequate	N/A	coating Packaging
III			3	Adequate	N/A	Packaging
III			3	Adequate	N/A	Packaging
III			3	Adequate	N/A	Packaging
III			3	Adequate	N/A	Packaging
III			3	Adequate	N/A	Packaging
III			3	Adequate	N/A	Packaging
III			3	Adequate	N/A	Packaging

b(4)

¹ 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")

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Joint Clinical/Safety/ Statistical	Preliminary: Approval	02-28-2009	Salma Lemtouni, M.D. Shona Pendse, Safety Reviewer Ququan Liu, Ph.D.
EES	Acceptable	04-07-2009	OC Overall Recommendation
Pharm/Tox	Approvable	11-06-2008	Gowra Jagadeesh, Ph.D.
OCPB	Acceptable	02-27-2009	Divya Menon-Andersen, Ph.D.
Methods Validation	Acceptable as per Review by Dr. Soldatova	03-03-2009	Lyudmila Soldatova, Ph.D.
DDMAC	Comments recommended for PPI	03-31-2009	Lisa Hubbard, R.Ph.
DMEPA	Comments for revision of labels are made	07-17-2009	Walter Fava, R.Ph.
EA	Adequate; FONSI is recommended	03-04-2009 03-05-2009	Raanan Bloom, Ph.D. (OPS/PARS)
CDTL Review	Recommended Approval	04-07-2009	Thomas Marciniak, MD



The Chemistry Review for NDA 22-314

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-314 for Exforge HCT 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, shelf-life of 24 months is recommended for all the strengths, 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, 10/320/25 mg in 30, 90 and 100 count (90 cc and 175 cc) bottles; and shelf life of 12 months is recommended for all dosage strengths in blister packs.

b(4)

The Exforge HCT tablets in 100 count (175 cc) bottles and in unit dose blister packages 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. The applicant has committed to provide complete updated specifications for five strengths of Exforge HCT tablets as a post-approval submission.

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 HCT film-coated tablets are immediate release dosage forms for oral administration. Exforge HCT Tablets is a fixed dose combination of three active ingredients, amlodipine, valsartan and hydrochlorothiazide. The label claims of amlodipine are expressed on the bases of free base. A total of five strengths of Exforge tablets, i.e., 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg (amlodipine/valsartan/ hydrochlorothiazide) are manufactured. The film coating, which is used to provide a distinctive tablet color for the different strengths. The inactive ingredients for all strengths of the tablets include microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, macrogol 4000 and talc. Additionally, individual tablet strengths contain titanium dioxide and/or yellow and red iron oxides. The coating premixes are a combination of ingredients which meet compendial or CFR requirements. The 5/160/12.5 mg and 10/160/12.5

b(4)



CHEMISTRY REVIEW



Executive Summary Section

mg strengths are compositionally similar with variation in the amount of _____ to keep the total tablet core weight at _____. Similarly, the 5/160/25 mg and 10/160/25 mg strengths are compositionally similar. The fifth strength, 10/320/25 is weight and dose proportional to the 5/160/12.5 mg strength with the same _____ being used for both. Novartis used their experience with Exforge tablets and Diovan HCT tablets to develop the triple combination. The product is manufactured by _____

b(4)

_____. The product will be marketed in _____ bottles _____, and _____

b(4)

_____. Standard specifications for solid oral dosage forms have been proposed similar to that for Exforge® Tablets; dissolution method and specification were found acceptable by ONDQA biopharm reviewer except for the dissolution specification for amlodipine for all dosage strengths; the final proposed dissolution specification for amlodipine with Q-value _____ in 30 minutes for all dosage strengths was accepted by the applicant. The updated regional (for US) specification including revised limits for water content, total impurities and dissolution is provided. The biowaiver is requested for the 5/160/25 mg, 10/160/12.5 mg and 10/320/25 mg strengths based on the results of bio-equivalency study (OCP Review dated 2/27/2009); biowaiver could be granted as per evaluation by ONDQA Biopharmaceutics reviewer. Three pilot scale batches of each strength in 30 count and 100 count _____ bottles have been placed on stability and a bracketing/ matrixing protocol has been used. The 12-month stability data has been submitted and a shelf life of 24 and _____ months is proposed for bottles and blisters, respectively, stored at 25°C. The 24-month expiry for drug product of all strengths in the _____ bottles _____ is acceptable. The 12-month shelf-life expiry _____ for drug product of all strengths in the _____ blister packaging could be granted based on the available 12-month stability data because of out-of-the specification stability data for dissolution and moisture at the accelerated storage conditions. _____

b(4)

b(4)

b(4)

b(4)

The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]; Recommendation "Protect from moisture. Dispense in tight container (USP)" is provided on the labels..

Three drug substances are used in the formulation of Exforge HCT tablets: valsartan, amlodipine besylate and hydrochlorothiazide. CMC information for valsartan is contained in Novartis' NDA for Diovan capsules (NDA 20-665) and subsequent supplements. Amlodipine besylate is obtained from three suppliers, _____

b(4)

_____ and DMFs for each are referenced for CMC information. The analytical comparison of batches from each supplier demonstrated that the drug substance batches from 3 sources are equivalent; the DMFs are adequate. Two suppliers of hydrochlorothiazide are listed _____

b(4)

_____. The analytical comparison of hydrochlorothiazide batches from these two suppliers demonstrated that sourced materials are equivalent; the drug substance from these suppliers is _____ by _____ Novartis. The respective hydrochlorothiazide DMFs are found adequate.

b(4)



Executive Summary Section

The overall Acceptable recommendation was assigned by OC for all drug substance and drug product facilities.

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

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

Exforge HCT tablets of different strengths are supplied as following available combinations: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg (amlodipine/ valsartan/ hydrochlorothiazide). All strengths are packaged in 30 and 90 count (90 cc and 175 cc, respectively) bottles; the 100 count bottles and unit dose blister packages are not planned to be marketed at this time. The drug will be administered orally.

b(4)

Dose is once-daily. Dosage may be increased after two weeks, as the maximum antihypertensive effect of Exforge HCT is reached within two weeks after a change in dose. The maximum recommended dose of Exforge HCT is 10/320/25 mg. Exforge HCT may be administered with or without food. Exforge HCT 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 overall recommendation for drug substance and drug product facilities from the Office of Compliance is Acceptable.

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: Scott N. Goldie, Ph.D.
Clinical Project Manager Name: Nguyen Quynh

C. CC Block

See DFS.

34 Page(s) Withheld

x Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Lyudmila Soldatova
4/17/2009 06:04:19 PM
CHEMIST

Ramesh Sood
4/20/2009 03:34:41 PM
CHEMIST

NDA 22-314

EXFORGE HCT

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 22-314
2. REVIEW #1
3. REVIEW DATE: March 3, 2009
4. REVIEWER: Lyudmila N Soldatova
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 74,490

Document Date

20-MAR-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Amendment

Document Date

28-JUN-2008

12-AUG-2008

25-AUG-2008

18-SEP-2008

15-OCT-2008

21-OCT-2008

21-NOV-2008

22-DEC-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Address: One Health Plaza
East Hanover, NJ 07936

Representative: Nancy A. Price
Executive Director, Drug regulatory Affairs



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Telephone: 862-778-3591

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Exforge HCT
- b) Non-Proprietary Name (USAN): amlodipine/valsartan/hydrochlorothiazide
- 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)(1)

10. PHARMACOL. CATEGORY: Hypertension

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg,
10/160/25 mg, 10/320/25 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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



CHEMISTRY REVIEW



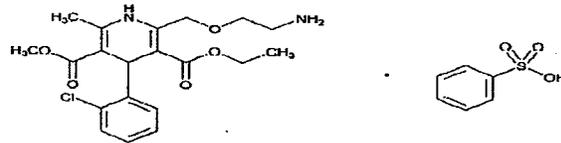
Chemistry Review Data Sheet

Amlodipine besylate

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

Molecular Formula: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

Molecular Weight: 567.05

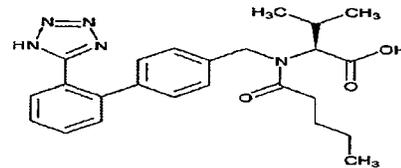


Valsartan

Chemical Name/USAN: *N*-[*p*-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine

Molecular Formula: $C_{24}H_{29}N_5O_3 \cdot C_6H_6O_3S$

Molecular Weight: 435.52

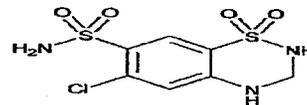


Hydrochlorothiazide

Chemical Name/USAN: 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Molecular Formula: $C_7H_8ClN_3OS_2$

Molecular Weight: 297.74



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	08-06-2008	Drug substance
	II			1	Adequate	09-26-2008	Drug substance
	II			1	Adequate	03-03-2009	Drug substance
	II			3	Adequate	05-12-2006	Drug substance
	II			3	Adequate	02-27-2008	Drug substance
	IV			3	Adequate	N/A	Tablet film coating
	III			3	Adequate	N/A	Packaging

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	III		3	Adequate	N/A	Packaging
	III		3	Adequate	N/A	Packaging
	III		3	Adequate	N/A	Packaging
	III		3	Adequate	N/A	Packaging
	III		3	Adequate	N/A	Packaging
	III		3	Adequate	N/A	Packaging
	III		3	Adequate	N/A	Packaging

b(4)

¹ 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")

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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

**CHEMISTRY REVIEW**

Chemistry Review Data Sheet

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical	Pending		Salma Lemtouni, M.D.
EES	Pending		
Pharm/Tox	Approvable	11-06-2008	Gowra Jagadeesh, Ph.D.
OCPB	Acceptable	02-27-2009	Divya Menon-Andersen, Ph.D.
Methods Validation	Acceptable as per this Review by Dr. Soldatova	03-03-2009	Lyudmila Soldatova, Ph.D.
DDMAC	Pending		Lisa Hubbard, R.Ph.
DMEPA	Acceptable	02-27-2009	Walter Fava, R.Ph.
EA	Adequate; FONSI is recommended	02-27-2009	Raanan Bloom, Ph.D. (OPS/PARS)
STATS	Pending		Cherry Liu, Ph.D.



The Chemistry Review for NDA 22-314

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-314 for Exforge HCT Tablets cannot be approved in its current form from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug product deficiencies, and upon the overall OC recommendation for drug substance and drug product manufacturing facilities. The applicant also has to submit the revised Novartis Test Specification for Amlodipine Besylate from _____

b(4)

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)

Exforge HCT film-coated tablets are immediate release dosage forms for oral administration. Exforge HCT Tablets is a fixed dose combination of three active ingredients, amlodipine, valsartan and hydrochlorothiazide. The label claims of amlodipine are expressed on the bases of free base. A total of five strengths of Exforge tablets, i.e., 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg (amlodipine/valsartan/ hydrochlorothiazide) are manufactured. The _____ film coating, which is _____, is used to provide a distinctive tablet color for the different strengths. The inactive ingredients for all strengths of the tablets include microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, macrogol 4000 and talc. Additionally, individual tablet strengths contain titanium dioxide and/or yellow and red iron oxides. The coating premixes are a combination of ingredients which meet compendial or CFR requirements. The 5/160/12.5 mg and 10/160/12.5 mg strengths are compositionally similar with variation in the amount of _____ to keep the total tablet core weight at _____. Similarly, the 5/160/25 mg and 10/160/25 mg strengths are compositionally similar. The fifth strength, 10/320/25 is weight and dose proportional to the 5/160/12.5 mg strength with the same _____ being used for both. Novartis used their experience with Exforge tablets and Diovan HCT tablets to develop the triple combination.

b(4)

b(4)



CHEMISTRY REVIEW



Executive Summary Section

The product will be marketed in _____ bottles

b(4)

Standard specifications for solid oral dosage forms have been proposed similar to that for Exforge® Tablets; dissolution method and specification were found acceptable by ONDQA biopharm reviewer except for the dissolution specification for amlodipine for all dosage strengths; it has to be revised by the applicant. The biowaiver is requested for the 5/160/25 mg, 10/160/12.5 mg and 10/320/25 mg strengths based on the results of bio-equivalency study (OCP Review dated 2/27/2009); biowaiver could be granted as per evaluation by ONDQA Biopharmaceutics reviewer. Three pilot scale batches of each strength have been placed on stability and a bracketing/ matrixing protocol has been used. The 12-month stability data has been submitted and a shelf life of 24 and _____ is proposed for bottles and blisters, respectively, stored at 25°C.

b(4)

The drug product is stored at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F). [See USP Controlled Room Temperature]; Recommendation "Protect from moisture. Dispense in tight container (USP)" is provided on the labels. The 24-month expiry for drug product of all strengths in the _____ bottles

_____ is acceptable.

b(4)

Three drug substances are used in the formulation of Exforge HCT tablets: valsartan, amlodipine besylate and hydrochlorothiazide. CMC information for valsartan is contained in Novartis' NDA for Diovan capsules (NDA 20-665) and subsequent supplements. Amlodipine besylate is obtained from three suppliers,

b(4)

_____ and DMFs for each are referenced for CMC information. The analytical comparison of batches from each supplier demonstrated that the drug substance batches from 3 sources are equivalent; the DMFs are adequate. Two suppliers of hydrochlorothiazide are listed,

b(4)

_____. The analytical comparison of hydrochlorothiazide batches from these two suppliers demonstrated that sourced materials are equivalent; the drug substance from these suppliers is _____ by _____ Novartis. The respective hydrochlorothiazide DMFs are found adequate.

b(4)

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

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

Exforge HCT tablets of different strengths are supplied as following available combinations: 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg (amlodipine/ valsartan/ hydrochlorothiazide). All strengths are packaged in bottles of 30, 90 and 100 count and unit dose blister packages _____ different sets of packaging configurations, Commercial, _____ are presented. The drug will be administered orally.

b(4)

**Executive Summary Section**

Dose is once-daily. Dosage may be increased after two weeks, as the maximum antihypertensive effect of Exforge HCT is reached within two weeks after a change in dose. The maximum recommended dose of Exforge HCT is 10/320/25 mg. Exforge HCT may be administered with or without food. Exforge HCT may be administered with other antihypertensive agents.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-314 for Exforge HCT Tablets cannot be approved in its current form from the CMC standpoint.

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: Scott N. Goldie, Ph.D.
Clinical Project Manager Name: Nguyen Quynh

C. CC Block

See DFS.

101 Page(s) Withheld

x Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Kasturi Srinivasachar
8/4/2008 02:52:48 PM
CHEMIST

Ramesh Sood
8/4/2008 03:23:59 PM
CHEMIST