

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200045Orig1s000

CHEMISTRY REVIEW(S)

NDA 200045

(Review #2)

Amturndie

(Aliskerin, Amlodipine, and Hydrochlorothiazide)

Tablets

**150/5/12.5mg, 300/5/12.5mg,
300/10/12.5mg, 300/5/25mg and 300/10/25mg**

Novartis Pharmaceuticals Corporation

Division of Cardio-renal Drug Products

Donghao (Robert) Lu, Ph.D.

Division of New Drug Quality Assessment I

Office of New Drug Quality Assessment

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer’s Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
Establishment Evaluation	11

Chemistry Review Data Sheet

1. **NDA 200045**
2. **REVIEW NUMBER:** 2
3. **REVIEW DATE:** 16 December 2010
4. **REVIEWER:** Donghao (Robert) Lu, Ph.D.
5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
--------------------	---------------

6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 200045	26-FEB-10
NDA 200045 (Amendment 002, specification)	06-APR-10
NDA 200045 (Amendment 005, stability)	23-JULY-10
NDA 200045 (Amendment 009, special supplement to NDA 21-985)	12-OCT-10
NDA 200045 (Amendment 010, CMC response)	13-OCT-10

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:	862-778-536

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	Amturndie
NON-PROPRIETARY NAME (USAN)	Aliskiren/Amlodipine besylate/ Hydrochlorothiazide
CODE NAME/ NUMBER (ONDC ONLY)	
CHEMISTRY TYPE / SUBMISSION PRIORITY	4S

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

10. PHARMACOL. CATEGORY: (1) Aliskiren - potent and selective inhibitor of human rennin
(2) Amlodipine - dihydropyridine calcium channel blocker
(3) Hydrochlorothiazide - diuretic and antihypertensive

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150/5/12.5mg, 300/5/12.5mg, 300/10/12.5mg, 300/5/25mg and 300/10/25mg (aliskiren/amlodipine /hydrochlorothiazide)

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: R_x OTC

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

SPOTS product – Form Completed
 Not a SPOTS product

Chemistry Assessment Section

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

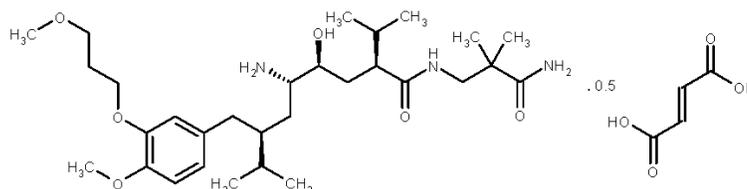
(1) Aliskiren hemifumarate

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.

Mol. Formula: $C_{30}H_{53}N_3O_6 \cdot 0.5 C_4H_4O_4$

Mol. Wt.: 609.8 (551.8 as free base)

Structural Formula:



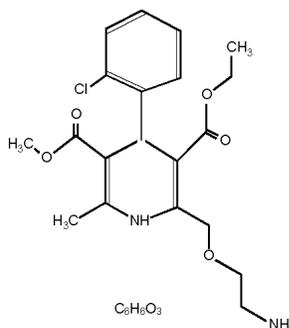
(2) Amlodipine besylate

Chemical name: 3-Ethyl-5-methyl (\pm)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate

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

Mol. Wt.: 567.1 (408.9 as free base)

Structural Formula:



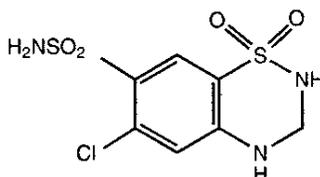
(3) Hydrochlorothiazide

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Mol. Formula: $C_7H_8ClN_3O_4S_2$

Mol. Wt.: 297.7

Structural Formula:



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	See NDA 22-545
	II		1	Adequate	See NDA 22-545	
	II		1	Adequate	See NDA 22-545	
	III		1	Adequate	9/15/2010	
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		

(b) (4)

Chemistry Assessment Section

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 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
NDA 21-985 (Tekturna Tablets)	NDA 21-985	Cross Reference (Aliskiren hemifumarate)
NDA 22-107 (Tekturna HCT Tablets)	NDA 22-107	Cross Reference (Aliskiren hemifumarate)
NDA 20-818 (Diovan HCT Tablets)	NDA 20-818	Cross Reference (Valsartan / hydrochlorothiazide)
NDA 22-314 (Exforge HCT Tablets)	NDA 22-314	Cross Reference (Valsartan, amlodipine besylate, hydrochlorothiazide)
NDA 22-545 (SPA100 Tablets)	NDA 22-545	Cross Reference (Aliskiren hemifumarate and amlodipine besylate)

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	16-DEC-10	E. Johnson
Methods Validation	No validation request	25-AUG-10	Donghao R. Lu, Ph.D.
ODS DMETS	Acceptable	30-NOV-10	K. Toliver, Pharm.D.
EA	Acceptable	8-DEC-10	R. A. Bloom, Ph.D.
Micro Consultation	N/A		

The Chemistry Review for NDA 200045

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, Amturndie (Aliskerin, Amlodipine, and Hydrochlorothiazide) Tablets, 150/5/12.5mg, 300/5/12.5mg, 300/10/12.5mg, 300/5/25mg and 300/10/25mg, is recommended as APPROVAL from a CMC perspective.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substances contained in the tablet products are aliskiren hemifumarate, amlodipine besylate and hydrochlorothiazide. The general information on the full names, chemical structures, molecular formulas and molecular weights can be seen on p. 4-5 above. Aliskiren hemifumarate is the drug substance described in NDA 21-985 for Tekturna Tablets as approved on March 5, 2007, and subsequent supplements. The manufacture of aliskiren hemifumarate drug substance was described in NDA 21-985, which is cross-referenced for this submission. Amlodipine besylate is the drug substance described in DMF (b) (4)

(b) (4) DMF (b) (4) have been concurrently reviewed to support NDA 22-545 (approved in August, 2010) and determined as adequate from CMC point of view. Hydrochlorothiazide is the drug substance described in NDA 20-818 for Diovan HCT Tablets as approved on March 6, 1998, and subsequent supplements. The manufacture of hydrochlorothiazide drug substance was described in NDA 20-818, which is cross-referenced for this submission.

Chemistry Assessment Section

2. Drug Product

The drug product is aliskiren/amlodipine/hydrochlorothiazide film-coated tablets (the code name is SAH100 tablets and the trade name is Amturndie tablets), in strengths of aliskiren/amlodipine/hydrochlorothiazide 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/10 mg/12.5 mg, 300 mg/5 mg/25 mg and 300 mg/10 mg/25 mg. Regardless of strength, the aliskiren/amlodipine/hydrochlorothiazide tablet manufacturing process consists of (b) (4)

(b) (4). The product is intended for oral administration. The aliskiren/amlodipine/hydrochlorothiazide tablets will be marketed in HDPE bottles with desiccant and child resistant closures, and in blisters. All five dosage strengths will have a 30 count packaging provided with a 90cc square HDPE bottle. In addition, the 150/5/12.5 mg strength tablet will be packaged in 90 and 100 counts with 120cc square HDPE bottles and the other four strengths (300/5/12.5 mg, 300/10/12.5 mg, 300/5/25 mg and 300/10/25 mg) will be packaged in 90 and 100 counts with 175cc square HDPE bottles. All strengths will also be packaged in 7 counts with 45cc round HDPE bottles as physician samples. The hospital packs will be provided in (b) (4) blister packs for all strengths. Inactive ingredients consist of microcrystalline cellulose/cellulose microcrystalline, crospovidone, povidone, colloidal silicon dioxide/silica (colloidal anhydrous), and magnesium stearate. (b) (4)

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

Amturndie (Aliskiren/amlodipine/hydrochlorothiazide) tablet product is a combination of direct renin inhibitor, dihydropyridine calcium channel blocker, and thiazide diuretic indicated for treatment of hypertension. However, this fixed combination drug is not indicated for initial therapy of hypertension. The administration dose is once-daily and it may be increased after two weeks of therapy. The maximum recommended dose is Aliskiren/amlodipine/hydrochlorothiazide 300/10/25 mg. With the maximal dose, the full blood pressure lowering effect was achieved 2 weeks after the treatment.

The combination drug product may be used to provide additional blood pressure lowering for patients not adequately controlled with any two of the following antihypertensive components: aliskiren, calcium channel blockers and diuretics. A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of this drug product may be switched to this drug product containing a lower dose of that component to achieve similar blood pressure reductions. Patients receiving aliskiren, amlodipine

Chemistry Assessment Section

and hydrochlorothiazide from separate tablets may receive a single tablet of this drug product containing the same component doses. Patients should establish a routine pattern for taking this drug product with regard to meals. The products should be stored at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F). The products have an expiration period (shelf life) of 24 months.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Novartis has submitted sufficient and appropriate information to support the approval of the drug product.

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

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

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/s/

DONGHAO R LU
12/16/2010

RAMESH K SOOD
12/16/2010

NDA 200045

**Aliskiren/Amlodipine/Hydrochlorothiazide
Tablets
150/5/12.5mg, 300/5/12.5mg,
300/10/12.5mg, 300/5/25mg and 300/10/25mg**

Novartis Pharmaceuticals Corporation

Division of Cardio-renal Drug Products

Donghao (Robert) Lu, Ph.D.

**Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
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C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block	10
Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	11
S. DRUG SUBSTANCE.....	11
P. DRUG PRODUCT	16
A. APPENDICES	59
R. REGIONAL INFORMATION	59
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	61
A. Labeling & Package Insert	61
B. Environmental Assessment Or Claim Of Categorical Exclusion	66
III. Establishment Evaluation Report.....	67
IV. List Of Comments.....	70

Chemistry Review Data Sheet

1. **NDA 200045**
2. **REVIEW NUMBER:** 1
3. **REVIEW DATE:** 18 OCTOBER 2010
4. **REVIEWER:** Donghao (Robert) Lu, Ph.D.
5. **PREVIOUS DOCUMENTS:**

PREVIOUS DOCUMENTS	DOCUMENT DATE
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6. **SUBMISSION(S) BEING REVIEWED:**

SUBMISSION REVIEWED	DOCUMENT DATE
NDA 200045	26-FEB-10
NDA 200045 (Amendment 002, specification)	06-APR-10
NDA 200045 (Amendment 005, stability)	23-JULY-10
NDA 200045 (Amendment 009, special supplement to NDA 21-985)	12-OCT-10
NDA 200045 (Amendment 010, CMC response)	13-OCT-10

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:	862-778-536

Chemistry Assessment Section

8. DRUG PRODUCT NAME/CODE/TYPE:

PROPRIETARY NAME	(b) (4)
NON-PROPRIETARY NAME (USAN)	Aliskiren/Amlodipine besylate/ Hydrochlorothiazide
CODE NAME/ NUMBER (ONDC ONLY)	
CHEMISTRY TYPE / SUBMISSION PRIORITY	4S

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

10. PHARMACOL. CATEGORY: (1) Aliskiren - potent and selective inhibitor of human rennin
(2) Amlodipine - dihydropyridine calcium channel blocker
(3) Hydrochlorothiazide - diuretic and antihypertensive

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150/5/12.5mg, 300/5/12.5mg, 300/10/12.5mg, 300/5/25mg and 300/10/25mg (aliskiren/amlodipine /hydrochlorothiazide)

13. ROUTE OF ADMINISTRATION: Oral

14. R_x/OTC DISPENSED: R_x OTC

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

SPOTS product – Form Completed
 Not a SPOTS product

Chemistry Assessment Section

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

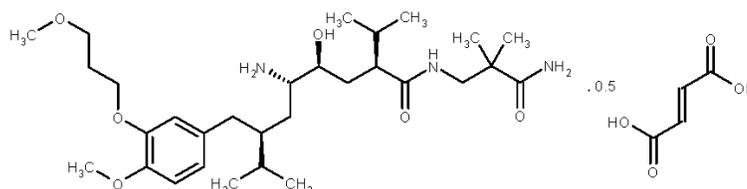
(1) Aliskiren hemifumarate

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.

Mol. Formula: $C_{30}H_{53}N_3O_6 \cdot 0.5 C_4H_4O_4$

Mol. Wt.: 609.8 (551.8 as free base)

Structural Formula:



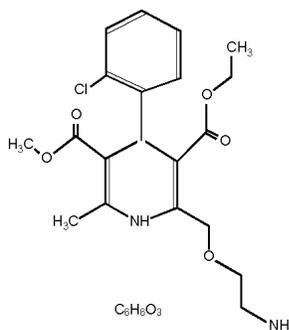
(2) Amlodipine besylate

Chemical name: 3-Ethyl-5-methyl (\pm)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate

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

Mol. Wt.: 567.1 (408.9 as free base)

Structural Formula:



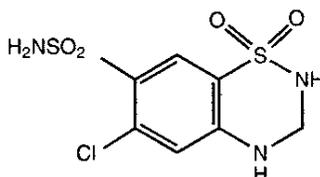
(3) Hydrochlorothiazide

Chemical name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

Mol. Formula: $C_7H_8ClN_3O_4S_2$

Mol. Wt.: 297.7

Structural Formula:



Chemistry Assessment Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	See NDA 22-545
	II		1	Adequate	See NDA 22-545	
	II		1	Adequate	See NDA 22-545	
	III		1	Adequate	9/15/2010	
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		
	III		4	N/A		

(b) (4)

Chemistry Assessment Section

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 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
NDA 21-985 (Tekturna Tablets)	NDA 21-985	Cross Reference (Aliskiren hemifumarate)
NDA 22-107 (Tekturna HCT Tablets)	NDA 22-107	Cross Reference (Aliskiren hemifumarate)
NDA 20-818 (Diovan HCT Tablets)	NDA 20-818	Cross Reference (Valsartan / hydrochlorothiazide)
NDA 22-314 (Exforge HCT Tablets)	NDA 22-314	Cross Reference (Valsartan, amlodipine besylate, hydrochlorothiazide)
NDA 22-545 (SPA100 Tablets)	NDA 22-545	Cross Reference (Aliskiren hemifumarate and amlodipine besylate)

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Methods Validation	No validation request	25-AUG-10	Donghao R. Lu, Ph.D.
ODS DMETS	Pending		
EA	Pending		
Micro Consultation	N/A		

The Chemistry Review for NDA 200045

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product, Aliskiren/Amlodipine/Hydrochlorothiazide Tablets, 150/5/12.5mg, 300/5/12.5mg, 300/10/12.5mg, 300/5/25mg and 300/10/25mg, is recommended as APPROVABLE from a CMC perspective, pending DMETS's, Office of Compliance's and EA's recommendations. A final memorandum will be submitted when these pending recommendations are received.

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

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

1. Drug Substance

The drug substances contained in the tablet products are aliskiren hemifumarate, amlodipine besylate and hydrochlorothiazide. The general information on the full names, chemical structures, molecular formulas and molecular weights can be seen on p. 4-5 above. Aliskiren hemifumarate is the drug substance described in NDA 21-985 for Tekturna Tablets as approved on March 5, 2007, and subsequent supplements. The manufacture of aliskiren hemifumarate drug substance was described in NDA 21-985, which is cross-referenced for this submission. Amlodipine besylate is the drug substance described in DMF (b) (4)

(b) (4) . DMF # (b) (4) have been concurrently reviewed to support NDA 22-545 (approved in August, 2010) and determined as adequate from CMC point of view. Hydrochlorothiazide is the drug substance described in NDA 20-818 for Diovan HCT Tablets as approved on March 6, 1998, and subsequent supplements. The manufacture of hydrochlorothiazide drug substance was described in NDA 20-818, which is cross-referenced for this submission.

Chemistry Assessment Section

2. Drug Product

The drug product is aliskiren/amlodipine/hydrochlorothiazide film-coated tablets (the code name is SAH100 tablets and the proposed trade name is (b) (4) tablets), in strengths of aliskiren/amlodipine/hydrochlorothiazide 150 mg/5 mg/12.5 mg, 300 mg/5 mg/12.5 mg, 300 mg/10 mg/12.5 mg, 300 mg/5 mg/25 mg and 300 mg/10 mg/25 mg. Regardless of strength, the aliskiren/amlodipine/hydrochlorothiazide tablet manufacturing process consists of (b) (4)

(b) (4). The product is intended for oral administration. The aliskiren/amlodipine/hydrochlorothiazide tablets will be marketed in HDPE bottles with desiccant and child resistant closures, and in blisters. All five dosage strengths will have a 30 count packaging provided with a 90cc square HDPE bottle. In addition, the 150/5/12.5 mg strength tablet will be packaged in 90 and 100 counts with 120cc square HDPE bottles and the other four strengths (300/5/12.5 mg, 300/10/12.5 mg, 300/5/25 mg and 300/10/25 mg) will be packaged in 90 and 100 counts with 175cc square HDPE bottles. All strengths will also be packaged in 7 counts with 45cc round HDPE bottles as physician samples. The hospital packs will be provided in (b) (4) blister packs for all strengths. Inactive ingredients consist of microcrystalline cellulose/cellulose microcrystalline, crospovidone, povidone, colloidal silicon dioxide/silica (colloidal anhydrous), and magnesium stearate. (b) (4)

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

Aliskiren/amlodipine/hydrochlorothiazide tablet product is a combination of direct renin inhibitor, dihydropyridine calcium channel blocker, and thiazide diuretic indicated for treatment of hypertension. However, this fixed combination drug is not indicated for initial therapy of hypertension. The administration dose is once-daily and it may be increased after two weeks of therapy. The maximum recommended dose is Aliskiren/amlodipine/hydrochlorothiazide 300/10/25 mg. With the maximal dose, the full blood pressure lowering effect was achieved 2 weeks after the treatment.

The combination drug product may be used to provide additional blood pressure lowering for patients not adequately controlled with any two of the following antihypertensive components: aliskiren, calcium channel blockers and diuretics. A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of this drug product may be switched to this drug product containing a lower dose of that component to achieve similar blood pressure reductions. Patients receiving aliskiren, amlodipine

Chemistry Assessment Section

and hydrochlorothiazide from separate tablets may receive a single tablet of this drug product containing the same component doses. Patients should establish a routine pattern for taking this drug product with regard to meals. The products should be stored at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F). The products have an expiration period (shelf life) of 24 months.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, Novartis has submitted sufficient and appropriate information to support the approval of the drug product. There were several CMC concerns that were sent to the sponsor on September 28, 2010. Novartis has adequately addressed these CMC comments. Their responses and the CMC evaluations for these responses are described in the corresponding sections.

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

\s\ Donghao (Robert) Lu, Ph.D.

B. Endorsement Block

\s\ Ramesh Sood, Ph.D.

C. CC Block

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/s/

DONGHAO R LU
10/20/2010

RAMESH K SOOD
10/22/2010

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	200045
Applicant:	Novartis
Letter Date:	25 Feb 2010
Stamp Date:	25 Feb 2010
PDUFA Date:	25 Dec 2010
Tradename:	(b) (4)
Established Name:	Aliskiren, amlodipine, hydrochlorothiazide
Dosage Form:	Tablets, 150/ 5/12.5 mg, 300/5/12.5 mg, 300/5/25, mg, 300/10/12.5 mg, 300/10/25 mg
Route of Administration:	Oral
Indication:	Hypertension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary

This is an e-CTD submission for a fixed dose combination of 3 drugs, aliskiren, amlodipine and hydrochlorothiazide. Aliskiren was originally developed by Novartis and marketed under the tradename Tekturna (NDA 21-985). Novartis later developed the combination products, Tekturna HCT (aliskiren/hydrochlorothiazide, NDA 22-107), Valturna (valsartan/aliskiren, NDA 22-217) and Tekamlo (amlodipine/aliskiren, pending NDA 22-545). Clinical trials for this triple combination were carried out under IND 101,386. The pivotal short term, active control trial evaluated the triple combination of aliskiren, amlodipine and HCTZ in comparison to the dual combinations, aliskiren/amlodipine, aliskiren/HCTZ and amlodipine/HCTZ. This and other supporting safety and efficacy studies were carried out using the free combinations of the individual drugs and bioequivalence /bioavailability studies have been used to bridge the results to the fixed dose product intended for marketing. A multidisciplinary pre-NDA meeting was scheduled for Mar 12, 2009 which included some CMC issues. In the preliminary responses from the Agency, Novartis was asked to submit representative COAs for both compendial and non-compendial excipients and to develop a specific ID test for inclusion in the drug product specification. Novartis proposed to submit limited stability data (3 months) for the 300/10/12.5 mg strength and 6 months' data for the other 4 strengths in the initial NDA submission and provide stability updates within (b) (4) months to support a 24 month expiry period. They were told to submit updates by month 5. The sponsor was recommended to include the physician sample bottles in their registration stability bracketing plan. Their proposal to perform stability studies on (b) (4) per strength for physician sample bottles was considered insufficient. 3 batches of each strength would be required unless their bracketing plan could cover this packaging configuration and the testing performed should be the same as for commercial configurations. No feedback was provided on the adequacy of the dissolution method or acceptance criteria; however, the Agency stated that a single dissolution method for all 3 drug components was acceptable in principle. Based on the preliminary responses, Novartis decide to cancel the face-to-face meeting scheduled for Mar 12, 2009.

Drug Substance

Three drug substances are used in the formulation of (b) (4)—aliskiren hemifumarate, amlodipine besylate and hydrochlorothiazide. CMC information for aliskiren is contained in Novartis' NDA for Tekturna tablets (21-985) and subsequent supplements. Amlodipine besylate is obtained from two suppliers, (b) (4) and DMFs for each are referenced for CMC information. Amlodipine besylate (b) (4) was used in Exforge tablets, NDA 21-990 and Exforge HCT tablets, NDA 22-314. The (b) (4) was last reviewed on Mar 4, 2010 and found to be adequate. A second DMF, (b) (4) for a new process. This DMF is currently under review in connection with pending NDA 22-545 by Novartis for the amlodipine/aliskiren combination. The (b) (4) was last reviewed on Feb 24, 2010 and concluded to be adequate; however, an information request letter was sent to the DMF holder. The DMF holder has not yet responded to this request. CMC information for hydrochlorothiazide is provided by cross-reference to the Novartis NDA, 20-818, for Diovan HCT tablets and subsequent supplements. For amlodipine besylate, Novartis has provided 2 separate testing monographs for the 2 suppliers and performed analytical comparison of batches from each. Their conclusion is that the drug substance batches from these 2 sources are equivalent.

Drug Product

(b) (4) film-coated tablets are immediate release dosage forms available in 5 strengths. (b) (4)



(b) (4) The product will be marketed in HDPE bottles with desiccant and child resistant closures as well as in (b) (4) blister packs. Three pilot scale batches of each strength have been placed on stability and a bracketing protocol based on tablet counts has been used. Limited data (up to 6 months) have been submitted and an initial shelf life of 12 and 9 months is proposed for bottles and blisters stored at 25°C. The stability studies will be updated during the review cycle with 12 months' long term data.

Critical Review Issues

Drug substance

- 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? Are the drug product batches manufactured representative of material from these sources?

Drug Product

- It is stated in the QOS that (b) (4) (b) (4)
- The ONDQA Biopharmaceutics team should be consulted for the dissolution method development and acceptance criteria. The biowaiver request for the 150/5/12.5 mg, 300/10/12.5 mg and 300/5/12.5 mg strengths based on the BE study for the 300/5/25 mg strength and the similarity in the in vitro dissolution profiles for each component in 4 different pH media should also be evaluated by this team.
- Have details been provided for the DOE to investigate variables (b) (4) ? What are the conclusions from these studies?
- How is (b) (4) assured during routine manufacture?
- A (b) (4) . Is this method suitable for resolving the 3 drug substances and their related substances from each other?
- Are the acceptance criteria for degradation products in conformance with ICH Q3B(R) recommendations?
- Impurity (b) (4) has been specified with a release and shelf-life limit of NMT (b) (4) . Is this a new amlodipine 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? Note: this issue was also included in the IQA for NDA 22-545 (Tekamlo).
- Degradation product (b) (4) . The limits have been set at NMT (b) (4) for release and shelf life. Are these limits acceptable based on

qualification studies and stability data? Note: this issue was also flagged in the IQA for NDA 22-545 (Tekamlo).

- Is the skip lot testing proposed for the microbial limits test acceptable?
- Is the proposed limit test (b) (4) acceptable? Is the acceptance criterion in accordance with the recommendations of the draft guidance?
- Is the bracketing of tablet counts in the stability protocol properly justified?
- Stability failures are observed for blister packs under accelerated conditions with degradation products outside the acceptance criteria. The expiration date assigned should take this into consideration.

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 for this application.

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Branch Chief

Apr.2, 2010
Date
Apr.2, 2010
Date

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200045

ORIG-1

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 (b) (4)

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/s/

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04/15/2010

RAMESH K SOOD
04/23/2010