CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-107

CHEMISTRY REVIEW(S)

All strengths of Tekturna HCT® Tablets are available in 30 and 90 counts in ——— bottles with desiccant and child resistant closures, and in blister packages (10 strips of 10 tablets). Based on the available stability data and statistical analysis provided, an expiry dating of 24 months for drug product packaged in ——— bottles with desiccant and 18 months packaged in ——— blisters is granted at the recommended storage condition: "Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86 °F). The granted expiry date, which was requested by the applicant, is fully supported by the provided (original and amendment) stability data. b(4)

All manufacturing sites have been found acceptable by Office of Compliance.

Recommended action: This NDA is recommended as **"Approval"** from CMC perspective.

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/s/

Ramesh Sood
1/7/2008 11:19:42 AM
CHEMIST

CHEMISTRY REVIEW

NDA 22-107

Tekturna HCT® (aliskiren and hydrochlorothiazide) Tablets, 150/12.5 mg, 150/25 mg, 300/12.5 and 300/25 mg

Novartis Pharmaceuticals Corporation

Xavier Ysern, PhD
ONDQA/ DPAI/ Branch II

(Clinical Review Division: DCRP)

Table of Contents

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA: 22-107

2. REVIEW #: 2

3. REVIEW DATE: 02-Jan-2008

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	20-Mar-2007
Amendment(s):	27-Mar-2007 (reference to NDA 20-818 CBE-30 Supplement, [redacted] HCTZ [redacted] properly referenced in amendment 30-May-2007)
	27-Apr-2007 (establishment information list)
	30-May-2007 (cross reference to NDA 20-818/S-037)
	17-Sep-2007 (additional stability data)

b(4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment(s):	19-Nov-2007 (response to 07-Nov-2007 Biopharm request)
	28-Nov-2007 (answers to CMC questions on November 21, 2007)
	12-Dec-2007 (answers to CMC questions on December 12, 2007)

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080 USA
Representative:	Kimberly Dickerson, Pharm. D. Assistance Director Drug Regulatory Affairs
Telephone:	(762) 778-4576

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Tekturna HCT® Tablets
b) Non-Proprietary Name (USAN):	Aliskiren/Hydrochlorothiazide Tablets
c) Code Name/# (ONDC only):	SPH100
d) Chem. Type/Submission Priority (ONDC only):	· Chem. Type: 4 (new combination) · Submission Priority: S (substantially equivalent)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Aliskiren and hydrochlorothiazide: Antihypertensive agent.
Hydrochlorothiazide: diuretic agent.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 150-/12.5-, 150-/25-, 300-/12.5- and 300-mg/25-mg

13. ROUTE OF ADMINISTRATION: Oral

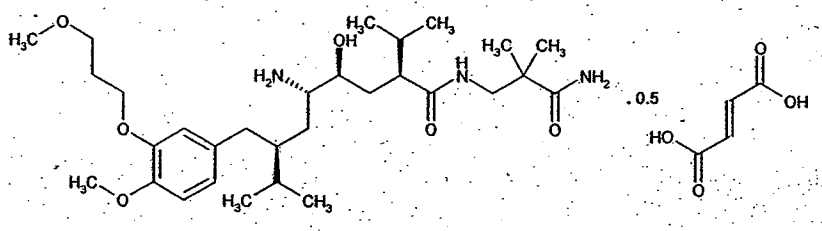
14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): Not a SPOTS product

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

Aliskiren fumarate

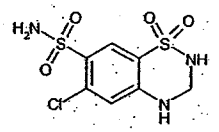
$C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$
MW: Salt form: 609.8
(551.8 as free base)
CAS registry #: 173334-58-2



(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

Hydrochlorothiazide

$C_7H_8ClN_3O_4S_2$
MW: 297.72
CAS registry #: 58-93-5



6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Holder	Item Referenced	Code[1]	Status[2]	LOA date	Comments
Type III			4	Adequate	03-Oct-2003	01-Nov-2001 update pp 1-126
			4	Adequate	21-Oct-2002	
			4	Adequate	28-Apr-2004	03-Mar-2002 update pp 5-9
			4	Adequate	01-Nov-2005	
			4	Adequate	07-Apr-2005	
			4	Adequate	09-Feb-2004	
			4	Adequate	11-Jul-2002	
			4	Adequate	16-Dec-2003	
			4	Adequate	21-Nov-2003	05-Apr-1993 page G-VII-b-1 05-Oct-1993 pages GII-a-1to4
			4	Adequate	18-Aug-2004	Section 107
			4	Adequate		Section 95
			4	Adequate	30-Jan-2006	Page E.2-2 Base film page E.1.a-8
Type IV			4	Adequate	05-May-2005	
			4	Adequate	05-May-2005	
			4	Adequate	05-May-2005	
			4	Adequate	05-May-2005	

[1] Action codes for DMF Table:

b(4)

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® (aliskiren) Tablets
NDA	20-818	Diovan HCT® (valsartan/ hydrochlorothiazide) Tablets
IND	62,976	Aliskiren monotherapy
IND	75,176	Aliskiren-Hydrochlorothiazide fixed dose combination

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	07-Aug-2007	S. Adams (HFD-322)
Pharm/Tox	--		
Biopharm	Pending		
Labeling (DDMAC)	Labeling issues still under review		
Methods Validation	Revalidation by Agency laboratories not recommended		
Tradename (DMATS)	Acceptability of tradename "Tekturna HCT®" Tablets still under review (multi disciplinary approach).		
EA	Acceptable		Part of this review
Microbiology	N.A.		

DDMAC = Division Drug Marketing, Advertising, and Communications; **DMETS** = Division of Medical Errors and Technical Support.

The Chemistry Review for NDA 22-107

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application can be APPROVED. All CMC pending issues have been addressed satisfactorily by the applicant (Amendments 28-Nov-2007 and 12-Dec-2007). Based on the stability data submitted, an expiry of 24 months for drug product packaged into ——— bottles with dessicant and 18 months packaged in ——— blisters is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Protect from moisture. b(4)

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

None.

II. Summary of Chemistry Assessments

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

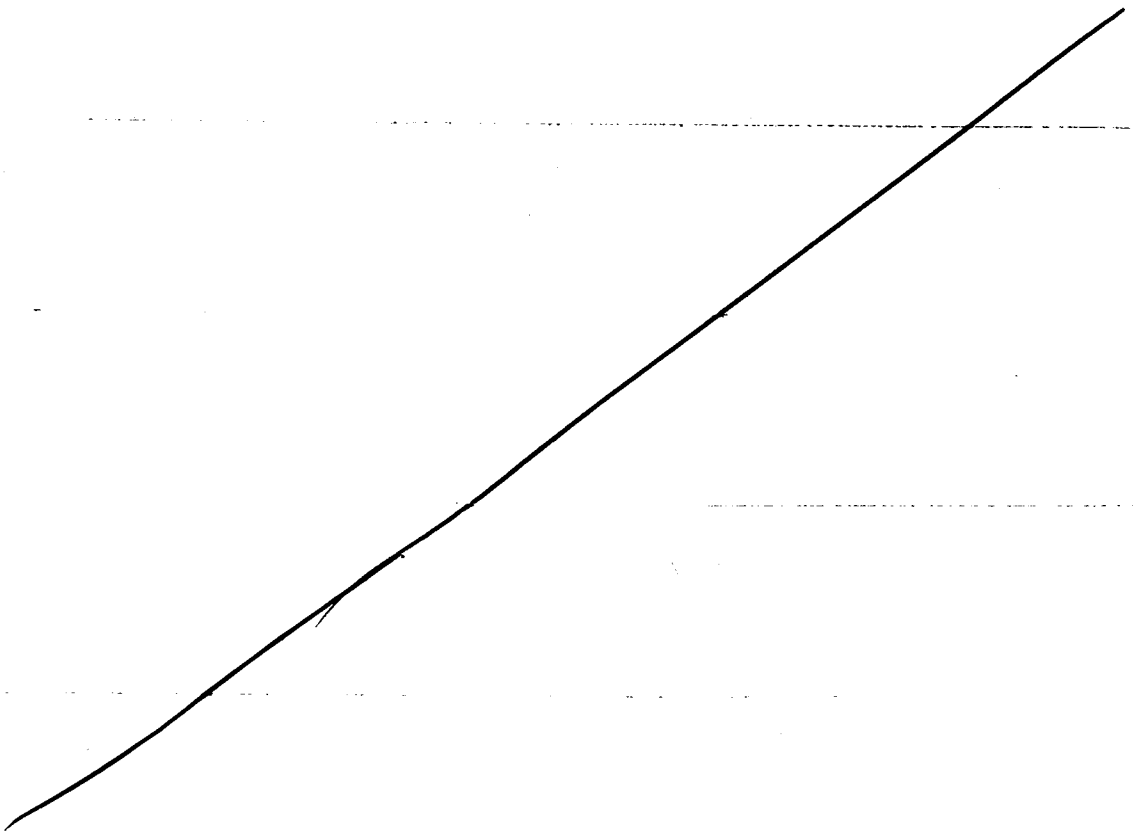
- Introduction

The drug product, Tekturna HCT® Tablets, is an immediate release solid oral dosage form that contains two active compounds, aliskiren and hydrochlorothiazide. Aliskiren and hydrochlorothiazide are hypotension agents that differ in both chemical class and mechanism of action. Drug products containing either aliskiren or hydrochlorothiazide are already in the market. The development of this fixed-dose combination drug product for the treatment of hypertension will facilitate patient compliance by reducing the number of dosage units and simplifying the treatment regime.

- Drug substances.

Hydrochlorothiazide (HCTZ), chemical name 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, has an empirical formula $C_7H_8ClN_3O_4S_2$ and a molecular weight of 297.72 g/mol. According to the Biopharmaceutics Classification System (BCS) hydrochlorothiazide is a class 3 (low permeability, high solubility) compound. HCTZ belongs to the thiazide class of diuretics, acting on the kidney to reduce sodium (Na) reabsorption in the distal convoluted tubule. Its mode of action as a diuretic and hypotensive agent is well known. Hydrochlorothiazide specifications conform to USP requirements. Hydrochlorothiazide is the drug substance of several approved drug products, including generic versions and combination products. HCTZ drug substance CMC information is cross referenced to applicant's approved NDA 20-818 Diovan HCT® (valsartan/ hydrochlorothiazide) Tablets.

Aliskiren (USAN), chemical 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-ethoxypropoxy)phenyl]octanamide, 551.8 Da molecular weight and $C_{30}H_{53}N_3O_6$ molecular formula, is a single diasteroisomer having 4 stereocarbons, all *S*-configurated. Aliskiren inhibits selectively the enzyme rennin, the first enzyme of the renin-angiotensin system (RAS). Aliskiren is the first in a novel class of renin inhibitors approved for the treatment of hypertension and related cardiovascular diseases (Tekturna® (aliskiren) Tablets, NDA 21-985). The active compound aliskiren is synthesized as it hemifumarate salt. Aliskiren hemifumarate is also the drug substance of Tekturna® (aliskiren) Tablets. Aliskiren hemifumarate drug substance CMC information is cross referenced to applicant's NDA 21-985 Tekturna® (aliskiren) Tablets approved on March 6, 2007.



b(4)

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

Tekturna HCT® is the combination tablet of aliskiren (Tekturna®), a renin inhibitor and hydrochlorothiazide (HCTZ), a diuretic. Tekturna HCT (aliskiren and hydrochlorothizide) Tablets, available in 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg dosage strengths, are intended for oral usage for the treatment of hypertension and are available. Aliskiren has been approved for treatment for hypertension in once daily doses of 150-300 mg while hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily. In clinical trials with Tekturna HCT® (aliskiren and hydrochlorothiazide, USP), using aliskiren doses of 75-300 mg and hydrochlorothiazide doses of 6.25 mg-25 mg, the antihypertensive effects increased with increasing doses. The usual recommended dose of Tekturna HCT® is one tablet once daily. The clinical response to Tekturna HCT® should be subsequently evaluated and if blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of aliskiren 300 mg/ hydrochlorothiazide 25mg.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf live. Based on the evaluation of the provided CMC information, from the chemistry viewpoint this NDA can be approved.

III. Administrative

A. Reviewer's Signature

Xavier Ysern, PhD	Chemist, ONDQA/ DPA I/ Branch II	Date: 02-Jan-2008

B. Endorsement Block

Ramesh Sood, PhD	Branch Chief, ONDQA/ DPA I/ Branch I	Date: 02-Jan-2008

C. CC Block

John David	Project Manager, OND/ ODE I/ DCRP

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3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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/s/

Xavier Ysern
1/7/2008 11:08:25 AM
CHEMIST

Ramesh Sood
1/7/2008 11:15:59 AM
CHEMIST

NDA 22-107

Tekturna HCT® (aliskiren and hydrochlorothiazide) Tablets, 150/12.5 mg, 150/25 mg, 300/12.5 and 300/25 mg

Novartis Pharmaceuticals Corporation

Xavier Ysern, PhD
ONDQA/ DPAI/ Branch II

(Clinical Review Division: DCRP)

Table of Contents

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA: 22-107

2. REVIEW #: 1

3. REVIEW DATE: 24-Oct-2007

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
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6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	20-Mar-2007
Amendment(s):	27-Mar-2007 (reference to NDA 20-818 CBE-30 Supplement, — HCTZ — properly referenced in amendment 30-May-2007) b(4)
	27-Apr-2007 (establishment information list)
	30-May-2007 (cross reference to NDA 20-818/S-037)
	17-Sep-2007 (additional stability data)

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza East Hanover, NJ 07936-1080 USA
Representative:	Kimberly Dickerson, Pharm. D. Assistance Director Drug Regulatory Affairs
Telephone:	(762) 778-4576

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Tekturna HCT® Tablets
b) Non-Proprietary Name (USAN):	Aliskiren/Hydrochlorothiazide Tablets
c) Code Name/# (ONDC only):	SPH100
d) Chem. Type/Submission Priority (ONDC only):	· Chem. Type: 4 (new combination) · Submission Priority: S (substantially equivalent)

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: Aliskiren and hydrochlorothiazide: Antihypertensive agent.
Hydrochlorothiazide: diuretic agent.

11. DOSAGE FORM: Tablets

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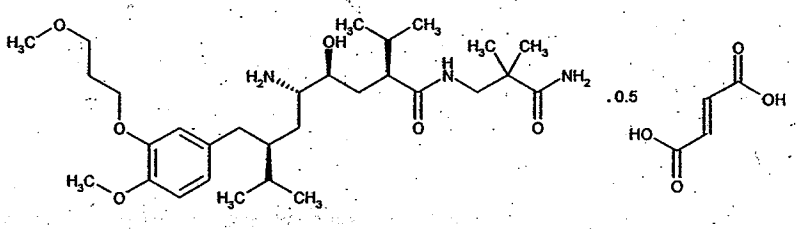

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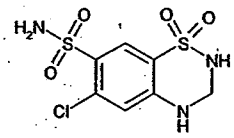

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			4	Adequate	16-Dec-2003	
			4	Adequate	21-Nov-2003	05-Apr-1993 page G-VII-b-1 05-Oct-1993 pages GII-a-1to4
			4	Adequate	18-Aug-2004	Section 107
			4	Adequate		Section 95
			4	Adequate	30-Jan-2006	Page E.2-2 Base film page E.1.a-8
Type IV			4	Adequate	05-May-2005	
			4	Adequate	05-May-2005	
			4	Adequate	05-May-2005	
			4	Adequate	05-May-2005	

b(4)

[1] Action codes for DMF Table:
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[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
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NDA	20-818	Diovan HCT® (valsartan/ hydrochlorothiazide) Tablets
IND	62,976	Aliskiren monotherapy
IND	75,176	Aliskiren-Hydrochlorothiazide fixed dose combination

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	07-Aug-2007	S. Adams (HFD-322) Summary report attached
Pharm/Tox	--		
Biopharm	Pending		
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories not recommended		
OPDRA			
EA	Acceptable		Part of this review
Microbiology	N.A.		

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The Chemistry Review for NDA 22-107

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application is APPROVABLE pending satisfactory response to the questions given under Basis for Approvability or Not-Approval Recommendation. Based on the stability data submitted, an expiry of 24 months for drug product packaged into ——— bottles with dessicant and 18 months packaged in ——— blisters is granted under the recommended storage conditions: Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) [see USP Controlled Room Temperature]. Protect from moisture. b(4)

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

None.

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- Drug substances.

Hydrochlorothiazide (HCTZ), chemical name 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, has an empirical formula $C_7H_8ClN_3O_4S_2$ and a molecular weight of 297.72 g/mol. According to the Biopharmaceutics Classification System (BCS) hydrochlorothiazide is a class 3 (low permeability, high solubility) compound. HCTZ belongs to the thiazide class of diuretics, acting on the kidney to reduce sodium (Na) reabsorption in the distal convoluted tubule. Its mode of action as a diuretic and hypotensive agent is well known. Hydrochlorothiazide specifications conform to USP requirements. Hydrochlorothiazide is the drug substance of several approved drug products, including generic versions and combination products. HCTZ drug substance CMC information is cross referenced to applicant's approved NDA 20-818 Diovan HCT® (valsartan/ hydrochlorothiazide) Tablets.

Aliskiren (USAN), chemical 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-ethoxypropoxy)phenyl]octanamide, 551.8 Da molecular weight and $C_{30}H_{53}N_3O_6$ molecular formula, is a single diasteroisomer having 4 stereocarbons, all *S*-configurated. Aliskiren inhibits selectively the enzyme rennin, the first enzyme of the renin-angiotensin system (RAS). Aliskiren is the first in a novel class of renin inhibitors approved for the treatment of hypertension and related cardiovascular diseases (Tekturna® (aliskiren) Tablets, NDA 21-985). The active compound aliskiren is synthesized as it hemifumarate salt. Aliskiren hemifumarate is also the drug substance of Tekturna® (aliskiren) Tablets. Aliskiren hemifumarate drug substance CMC information is cross referenced to applicant's NDA 21-985 Tekturna® (aliskiren) Tablets approved on March 6, 2007.

[redacted]

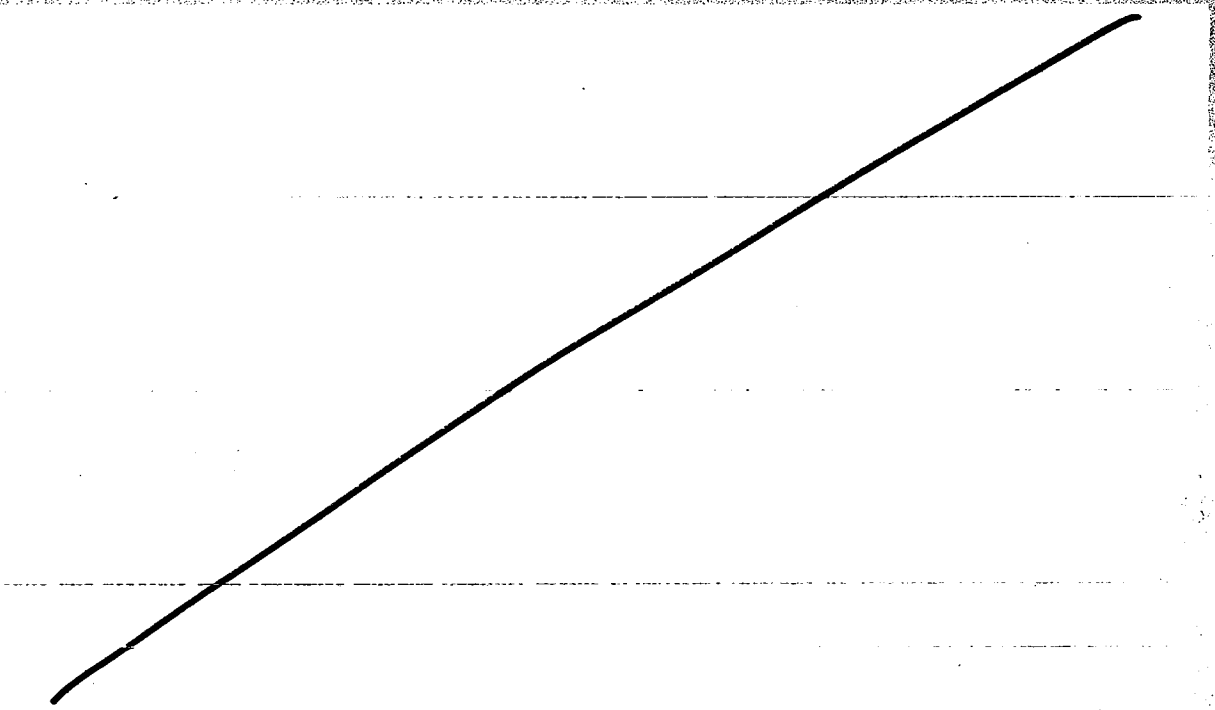
b(4)

- Drug Product

The drug product Tekturna HCT® Tablets (SPH100 film coated tablets), is a combination product of two active components aliskiren and hydrochlorothiazide (HCTZ) formulated as immediate release coated tablets. Four dose combinations of aliskiren and HCTZ are proposed for marketing: 150/12.5 mg, 150/25 mg, 300/12.5, and 300/25 mg. The formulations contain aliskiren hemifumarate (SPP100) and hydrochlorothiazide (active components, cellulose microcrystalline [redacted] crospovidone [redacted] lactose [redacted] wheat starch [redacted] povidone [redacted] magnesium stearate [redacted], silica colloidal [redacted], talc [redacted], and [redacted] titanium dioxide, iron oxide [redacted], iron oxide [redacted], iron oxide [redacted] PEG [redacted] Hypromellose [redacted] and Talc. All excipients, including the components of the different [redacted], meet compendial requirements.

[redacted]

b(4)



b(4)

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b(4)

All strengths of Tekturna HCT® Tablets are available in bottles with desiccant and child resistant closures of 30 and 90 counts, and in blister packages (10 strips of 10 tablets). Based on the available stability data and statistical analysis provided, an expiry dating of 24 months for drug product packaged into bottles with desiccant and 18 months packaged in Alu blisters is granted at the recommended storage condition: "Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86 °F). The granted expiry date, which was requested by the applicant, is fully supported by the provided (original and amendment) stability data.

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

Tekturna HCT® is the combination tablet of aliskiren (Tekturna®), a renin inhibitor and hydrochlorothiazide (HCTZ), a diuretic. Tekturna HCT (aliskiren and hydrochlorothizide) Tablets, available in 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg dosage strengths, are intended for oral usage for the treatment of hypertension and are available. Aliskiren has been approved for treatment for hypertension in once daily doses of 150-300 mg while hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily. In clinical trials with Tekturna HCT® (aliskiren and hydrochlorothiazide, USP), using aliskiren doses of 75-300 mg and hydrochlorothiazide doses of 6.25 mg-25 mg, the antihypertensive effects increased with increasing doses. The usual recommended dose of Tekturna HCT® is one tablet once daily. The clinical response to Tekturna HCT® should be subsequently evaluated and if blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to a maximum of aliskiren 300 mg/ hydrochlorothiazide 25mg.

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been submitted to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and recommendations given in the original submission and pertinent amendments were shown, judged by compliance to their proposed specifications, to assure their quality throughout shelf live. Based on the evaluation of the provided CMC information, from the chemistry viewpoint this NDA can be approved after satisfactory response to the following requests:

69 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

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/s/

Xavier Ysern
11/20/2007 03:09:26 PM
CHEMIST

Ramesh Sood
11/20/2007 03:12:05 PM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-107
Applicant:	Novartis
Letter Date:	19 Mar 2007
Stamp Date:	20 Mar 2007
PDUFA Date:	20 Jan 2008
Tradename:	Tekturna HCT
Established Name:	Aliskiren and hydrochlorothiazide
Dosage Form:	Film Coated Tablets, 150/12.5 mg, 150/25 mg, 300/12.5 mg, 300/25 mg, aliskiren/hydrochlorothiazide
Route of Administration:	Oral
Indication:	Hypertension
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes
Comments for 74-Day Letter:	None at this time

Summary

This NDA is an electronic submission in CTD format for a fixed dose combination product of aliskiren, a renin inhibitor and hydrochlorothiazide, a diuretic. Aliskiren was very recently approved as monotherapy for the treatment of hypertension (NDA 21-985, approved Mar 5, 2007) whereas hydrochlorothiazide is a well established diuretic used alone or in combination with several classes of anti-hypertensives.

The clinical program in support of this NDA was conducted under IND applications 62,976 and 75,176. The Applicant submitted a Special Protocol Assessment for their proposed stability bracketing and matrixing design which was initially found to be unacceptable. After a follow up teleconference with the firm and significant revisions, the protocol was accepted.

Drug Substance

The combination tablets contain aliskiren as the hemifumarate salt and CMC information concerning this drug substance has been cross referenced to NDA 21-985 which was reviewed by Xavier Ysern (see Reviews #1 and 2 in DFS). Aliskiren hemifumarate belongs to BCS Class 3 (high solubility, low permeability), is hygroscopic and crystallizes in fine needles.

For the hydrochlorothiazide component, the Applicant refers to their NDA 20-818 and its supplements for complete CMC information. There is an USP monograph for hydrochlorothiazide, a white crystalline powder which is slightly soluble in water.

Drug Product

This is an immediate release product which will be marketed in the 4 strengths listed above. A film coating is needed for the tablets to mask the bitter taste of aliskiren and to achieve dose differentiation of the various strengths by different colors. Based on their recent experience

formulating the aliskiren hemifumarate monotherapy product and their manufacture of combination drug products containing hydrochlorothiazide, Novartis has opted for a process

[redacted] b(4)

[redacted] : 75/12.5 mg and 150/25 mg
[redacted] : 300/12.5 mg
[redacted] 150/12.5 mg and 300/25 mg.

[redacted] b(4)

Critical Issues for Review

Drug Substance

- The Applicant has committed to incorporate a test for assay in the specification for [redacted], a starting material in the synthesis of aliskiren hemifumarate (NDA 21-985). The reviewer should confirm that Novartis has implemented this test and that the acceptance criterion proposed is reasonable. b(4)
- Subsequent to the original NDA submission the Applicant has submitted a "CBE-30 Supplement" for a change in batch size for the [redacted] of HCTZ at Novartis' Schweizerhalle AG facility. Obviously, a supplement cannot be submitted to a pending NDA. They should either convert this to an Amendment or cross-reference a supplement to NDA 20-818 (Diovan HCT) for this change. b(4)

Drug Product

- It is stated in the QOS that [redacted] and of the [redacted] has been demonstrated by [redacted] However, the in-process tests listed measure only [redacted] b(4)
- Dissolution is a critical quality attribute of product performance. Is the method discriminatory? The acceptance criteria proposed raise some obvious concerns – the aliskiren monotherapy NDA has Q= [redacted] in 30 min whereas Q= [redacted] in 45 min is proposed for the dissolution of aliskiren in the combination product. Is this justified? In addition, for the HCTZ component, different release and shelf-life limits are proposed which is unusual for dissolution. The shelf-life limit of Q= [redacted] in 60 min conforms to the USP monograph for HCTZ tablets, however, most combination drug products b(4)

containing HCTZ have Q= [redacted] in 30 min (see, for example, USP for enalapril HCTZ tablets and the Applicant's own NDA 20-818 for Diovan HCT).

- The limit for residual [redacted] in the drug product specification is [redacted] whereas in the Tekturna NDA (21-985) the approved limit is [redacted] Since [redacted] is used only in the manufacture of aliskiren hemifumarate granulate, is there adequate justification for the proposed higher limit? b(4)
- One of the strengths (300/12.5 mg) is described as violet white tablets – is this an accurate description?

Comments and Recommendations

The application is fileable. Facilities have not yet been entered into EES since the Applicant has not provided a list of manufacturing and testing sites for the 2 drug substances. They have been contacted about this issue and requested to amend the application with a complete list of all establishments. A single CMC reviewer is recommended for this NDA which contains mainly drug product information and Dr Xavier Ysern who reviewed Tekturna would be ideal.

Kasturi Srinivasachar — Apr 26, 2007
Pharmaceutical Assessment Lead — Date

Ramesh Sood, Ph.D. — Apr 26, 2007
Branch Chief — Date

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/s/

Kasturi Srinivasachar
4/26/2007 02:01:10 PM
CHEMIST

Ramesh Sood
4/26/2007 02:55:55 PM
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