CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-985

CHEMISTRY REVIEW(S)

NDA 21-985

Tekturna®
(Aliskiren) Tablets

DIVISION DIRECTOR REVIEW #2

Applicant: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Indication: Proposed for the treatment of hypertension as monotherapy or in combination with other antihypertensive agents.

Presentation: Supplied as 150 mg and 300 mg strength, immediate release, film-coated tablets in — bottles, 30 or 90 count, and in unit-dose — olister packages, 100 count (10 strips of 10 tablets each).

EER Status: Acceptable 08-MAR-2006

Consults: Clinical Pharmacology – Acceptable 10-JAN-2007
EA - Finding of No Significant Impact 20-MAY-2006 OPS
Methods Validation – Agency revalidation not recommended
Labeling - under review (multi-disciplinary approach)

Original Submission: 10-FEB-2006

Post-Approval Agreements:

1. The applicant has agreed to establish an assay method and acceptance criterion for — (SPP100 — Assay method and assay specification will be introduced into the testing monograph No. RM_5000702 for — post-approval by March 2007. The revised testing monograph will be submitted to FDA in the first NDA Annual Report.

2. The applicant has agreed to re-evaluate the specifications for the — when further data are available from the additional manufacturing sites. Novartis expects to have this data evaluation completed by June 2007.

Drug Substance:

Aliskiren is a new molecular entity (NME). A renin inhibitor, aliskiren hemifumarate is a chiral molecule named (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. The drug substance, aliskiren hemifumarate , is characterized as a white to slightly yellowish powder, is very hygroscopic, , and has a molecular formula of $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$ giving rise to a molecular weight of 551.8 Da (free base) and 609.8 Da (salt). It is highly soluble in water (>350 mg/mL) and —

. It has been classified as a class 3 compound according to the Biopharmaceutics Classification System (high solubility, low permeability).

Aliskiren was a developed by a structure-based drug design approach. The applicant combined molecular modeling and crystallographic structural analysis to design renin inhibitors. The drug substance, aliskiren hemifumarate, is derived synthetically

. With four chiral carbon centers, 16 stereoisomers of the molecule are possible. Aliskiren is a single diastereoisomer with all four chiral centers being S-configured.

Aliskiren was characterized and structurally elucidated using conventional and well established spectroscopic techniques including

Drug substance specifications include

Reference standard for Aliskiren has been developed and characterized.

A retest period of , under storage at < 25 °C, in bags, with a , and protected from light., is recommended.

Conclusion: Drug substance is satisfactory.

Drug Product:

The drug product is an immediate release, film-coated tablet for oral administration of either 150 mg or 300 mg strength, with the following description:

> The 150-mg tablets are light pink, biconvex round tablets, no scoring, with one side with "IL" and the other with "NVR."
>
> The 300-mg tablets are light red, biconvex ovaloid tablets, no scoring, with one side with "UL" and the other with "NVR."

The composition of the 150-mg strength core tablet is ng of aliskiren hemifumarate (active) (, w/w), mg cellulose microcrystalline mg crospovidone mg Povidone mg magnesium stearate mg Colloidal Silicon Dioxide, a total uncoated tablet weight of The composition of the 300 mg strength core tablet is dose proportional for a total uncoated tablet weight of (include: titanium oxide, iron oxide , polyethylene glyco nd

hydroxypropylmethyl cellulose (hypromellose). All drug product components meet compendial requirements.

Drug product specification includes [redacted]. All test methods have been appropriately validated for their intended purposes.

The requested expiration dating of 24 months at 25 °C (77 °F), excursions permitted to 15-30 °C (59-86 °F) for the drug product packaged in [redacted] bottles, protected from moisture, and for drug product packaged in the proposed blister package, is recommended. An in-use period was established to be [redacted] after first opening of [redacted] bottles, 30 count, and [redacted] after first opening of [redacted] 90 count.

Conclusion: Drug product is satisfactory.

Additional Items:

The sponsor commits to conduct the necessary stability studies on the first three commercial batches of Tekturna® (Aliskiren) 150-mg and 300-mg film-coated tablets.

The applicant also commits one batch of Tekturna® (Aliskiren) 150-mg and 300-mg film-coated tablets to be placed on stability annually and tested according to the protocol described therein through the expiry period.

All associated Drug Master Files (DMFs) are adequate.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval**, pending agreement on product labeling.

Blair Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
2/14/2007 07:17:12 AM
CHEMIST

NDA 21-985

Tekturna® (Aliskiren) Tablets

Novartis Pharmaceuticals Corporation

Xavier Ysern, PhD
ONDQA/ DPA I

(NDA Clinical Review Division: DCRP)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-985

2. REVIEW #: 3

3. REVIEW DATE: 30-NOV-2006

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 62,976	18-NOV-2002
Original NDA 21-985	10-FEB-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	29-NOV-2006

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® (originally proposed as Rasilez®)
b) Non-Proprietary Name (USAN):	Aliskiren
c) Code Name/# (ONDC only):	SPP100
d) Chem. Type/Submission Priority:	
· Chem. Type:	Type 1
· Submission Priority:	S

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

10. PHARMACOL. CATEGORY: Renin inhibitor. Proposed for the treatment of hypertension alone and in combination with other antihypertensive agents

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150-mg and 300-mg

13. ROUTE OF ADMINISTRATION: Oral

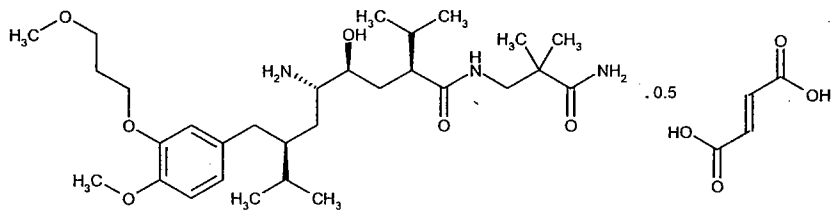
14. Rx/OTC DISPENSED: _x_Rx ___OTC

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:

Aliskiren hemifumarate

$C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$
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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

#	Holder	Item referenced	Code[1]	Status[2]	LOA	Date review	Comments
Type IV							
			4	Adequate	05May05		p. 4147 10Mar2000 p. 4146 10Mar2000 p. 4145 10Mar2000 p. 4145 10Mar2000
Type III							
			4	Adequate			
			4	Adequate	03Oct03		
			4	Adequate	21Oct02		
			4	Adequate	28Apr04		
			4	Adequate	07Apr05		p. 4-8 07Dec1995
			4	Adequate	09-Feb04		p. 5-10 01Apr1997
			4	Adequate	11Jul02		
			4	Adequate	16Dec03		
			4	Adequate	18Aug04		
			4	Adequate	18Mar03		

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
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18. **STATUS:**

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	08-MAR-2006	EER Summary report attached
Pharm/Tox	N.A.		
Biopharm	Adequacy of the dissolution specification Pending decision*		
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories not recommended		
OPDRA			
EA	Satisfactory. Finding of No Significant Impact	20-MAY-2006	Bai Nguyen, Chemist, OPS, HFD-354
Microbiology	N.A.		

* See page 9 of CMC Review # 2.

The Chemistry Review for NDA 21-985

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application can be APPROVED. Based on the stability data submitted, an expiry of 24 months 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. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant, Novartis, has agreed to the following commitments:

1. To establish an assay method and acceptance criterion for — (SPP100 — Assay method and assay specification will be introduced into the testing monograph No. RM_5000702 for — post approval by March 2007. The revised testing monograph will be submitted to FDA in the first NDA Annual Report.
2. To re-evaluate the specifications for the —— when further data are available from the additional manufacturing sites. Novartis expects to have this data evaluation completed by June 2007.

II. Summary of Chemistry Assessments

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

Refer to NDA 21-985 CMC Review # 1.

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

Refer to NDA 21-985 CMC Review # 1.

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

B. Endorsement Block

Xavier Ysern, PhD	Chemist, ONDQA/ DPA I/ Branch II	Date: 30-NOV-2006
Ramesh Sood, PhD	Branch Chief, ONDQA/ DPA I/ Branch I	Date: 30-NOV-2006

C. CC Block

1 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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/s/

Xavier Ysern
12/21/2006 04:06:52 PM
CHEMIST

Ramesh Sood
12/21/2006 04:45:54 PM
CHEMIST

NDA 21-985

Tekturna® (Aliskiren) Tablets

DIVISION DIRECTOR REVIEW

Applicant: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Indication: Proposed for the treatment of hypertension as monotherapy or in combination with other antihypertensive agents.

Presentation: Supplied as 150 mg and 300 mg strength tablets in — bottles, 30 or 90 count, and in — blister packages, 100 count.

EER Status: Acceptable 08-MAR-2006

Consults: Clinical Pharmacology - Dissolution specification **Pending**
EA - Finding of No Significant Impact 20-MAY-2006 OPS
Methods Validation – Agency revalidation not recommended
Labeling - under review (multi disciplinary approach)

Original Submission: 10-FEB-2006

Post-Approval Agreements:

The applicant, Novartis, has agreed to the following commitments:

1. To establish an assay method and acceptance criterion for — (SPP100 —. Assay method and assay specification will be introduced into the testing monograph No. RM_5000702 for — post-approval by March 2007. The revised testing monograph will be submitted to FDA in the first NDA Annual Report.

2. To re-evaluate the specifications for the — when further data are available from the additional manufacturing sites. Novartis expects to have this data evaluation completed by June 2007.

Drug Substance:

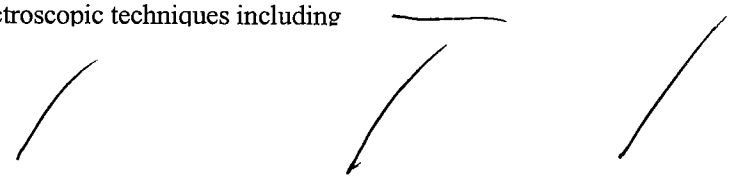
Aliskiren is a new molecular entity (NME). A renin inhibitor, aliskiren hemifumarate is a chiral molecule named (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3- methoxypropoxy)phenyl]octanamide hemifumarate. The drug substance, aliskiren hemifumarate , is characterized as a white to slightly yellowish powder, is very hygroscopic, and has a molecular formula of $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$ giving rise to a molecular weight of 551.8 Da (free base) and 609.8 Da (salt). It is highly soluble in water (>350 mg/mL) and less soluble in

. It has been classified as a class 3 compound according to the Biopharmaceutics Classification System (high solubility, low permeability).

Aliskiren was a developed by a structure-based drug design approach. The applicant combined molecular modeling and crystallographic structural analysis to design renin inhibitors. The drug substance, aliskiren hemifumarate, is derived synthetically

With four chiral carbon centers, 16 stereoisomers of the molecule are possible. Aliskiren is a single diastereoisomer with all four chiral centers being S-configured.

Aliskiren was characterized and structurally elucidated using conventional and well established spectroscopic techniques including



Drug substance specifications include

Reference standard for Aliskiren has been developed and characterized.

A retest period of under storage at < 25 °C, in bags, with a protected from light.

Conclusion: Drug substance is satisfactory.

Drug Product:

The drug product is an immediate release, film-coated tablet for oral administration of either 150 mg or 300 mg strength, with the following description:

> The 150-mg tablets are light pink, biconvex round tablets, no scoring, with one side with "IL" and the other with "NVR."
>
> The 300-mg tablets are light red, biconvex ovaloid tablets, no scoring, with one side with "IL" and the other with "NVR."

The composition of the 150-mg strength core tablet is mg of aliskiren hemifumarate (active) mg cellulose microcrystalline mg crospovidone Povidone mg magnesium stearate mg Colloidal Silicon Dioxide, a total uncoated tablet weight of The composition of the 300 mg strength core tablet is dose proportional for a total uncoated tablet weight of titanium oxide, iron oxide , polyethylene glycol and hydroxypropylmethyl cellulose (hypromellose). All drug product components meet compendial requirements.

Drug product specifications include : [redacted]

All test methods have been appropriately validated for their intended purposes.

Submitted real-time stability data and accelerated stability data support the proposed expiration dating of 24 months at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F) for the drug product packaged in [redacted] bottles, protected from moisture, and 24 months for drug product packaged in the proposed blister package. In-use period was established to be [redacted] after first opening of [redacted] bottles, 30 count, and [redacted] after first opening of [redacted], 90 count.

Conclusion: Drug product is satisfactory.

Additional Items:

The sponsor commits to conduct the necessary stability studies on the first three commercial batches of Tekturna® (Aliskiren) 150-mg and 300-mg film-coated tablets.

The applicant also commits one batch of Tekturna® (Aliskiren) 150-mg and 300-mg film-coated tablets to be placed on stability annually and tested according to the protocol described therein through the expiry period.

All associated Drug Master Files (DMFs) are adequate.

CMC labeling is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval.**

Blair Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
12/12/2006 12:18:39 PM
CHEMIST

NDA 21-985

Tekturna® (Aliskiren) Tablets

Novartis Pharmaceuticals Corporation

Xavier Ysern, PhD
ONDQA/ DPA I

(NDA Clinical Review Division: DCRP)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-985

2. REVIEW #: 2

3. REVIEW DATE: 16-NOV-2006

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 62,976	18-NOV-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10-FEB-2006
Amendment	14-NOV-2006 (response to CMC questions)

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® (originally proposed as Rasilez®)
b) Non-Proprietary Name (USAN):	Aliskiren
c) Code Name/# (ONDC only):	SPP100
d) Chem. Type/Submission Priority:	
· Chem. Type:	Type 1
· Submission Priority:	S

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

10. PHARMACOL. CATEGORY: Renin inhibitor. Proposed for the treatment of hypertension alone and in combination with other antihypertensive agents

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150-mg and 300-mg

13. ROUTE OF ADMINISTRATION: Oral

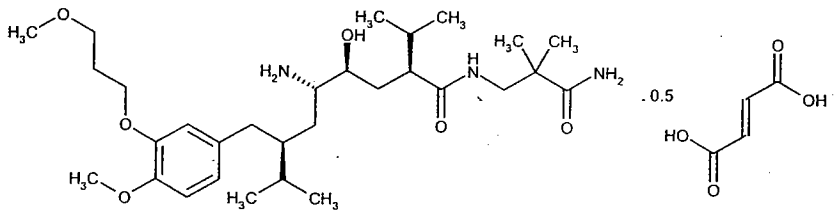
14. Rx/OTC DISPENSED: _x_Rx ___OTC

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:

Aliskiren hemifumarate

$C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$
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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

#	Holder	Item referenced	Code[1]	Status[2]	LOA	Date review	Comments
Type IV							
			4	Adequate	05May05		p. 4147 10Mar2000 p. 4146 10Mar2000 p. 4145 10Mar2000 p. 4145 10Mar2000
Type III							
			4	Adequate			
			4	Adequate	03Oct03		
			4	Adequate	21Oct02		
			4	Adequate	28Apr04		
			4	Adequate	07Apr05		p. 4-8 07Dec1995
			4	Adequate	09-Feb04		p. 5-10 01Apr1997
			4	Adequate	11Jul02		
			4	Adequate	16Dec03		
			4	Adequate	18Aug04		
			4	Adequate	18Mar03		

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
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18. **STATUS:**

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	08-MAR-2006	EER Summary report attached
Pharm/Tox	N.A.		
Biopharm	Adequacy of the dissolution specification Pending decision		
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories not recommended		
OPDRA			
EA	Satisfactory. Finding of No Significant Impact	20-MAY-2006	Bai Nguyen, Chemist, OPS, HFD-354
Microbiology	N.A.		

The Chemistry Review for NDA 21-985

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view this application can be APPROVED. Based on the stability data submitted, an expiry of 24 months 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. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant, Novartis, has agreed to the following commitments:

1. To establish an assay method and acceptace criterion for — (SPP100 — Assay method and assay specification will be introduced into the testing monograph No. RM_5000702 for — post approval by March 2007. The revised testing monograph will be submitted to FDA in the first NDA Annual Report.
2. To re-evaluate the specifications for the — when further data are available from the additional manufacturing sites. Novartis expects to have this data evaluation completed by June 2007.

II. Summary of Chemistry Assessments

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

Refer to NDA 21-985 CMC Review # 1.

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

Refer to NDA 21-985 CMC Review # 1.

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

B. Endorsement Block

Xavier Ysern, PhD	Chemist, ONDQA/ DPA I/ Branch II	Date: 16-NOV-2006
Ramesh Sood, PhD	Branch Chief, ONDQA/ DPA I/ Branch I	Date: 16-NOV-2006

C. CC Block

4 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Xavier Ysern
11/20/2006 10:01:04 AM
CHEMIST

Ramesh Sood
11/20/2006 04:00:24 PM
CHEMIST

NDA 21-985

Tekturna® (Aliskiren) Tablets

Novartis Pharmaceuticals Corporation

Xavier Ysern, PhD
ONDQA/ DPA I

(NDA Clinical Review Division: DCRP)

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-985

2. REVIEW #: 1

3. REVIEW DATE: 26-OCT-2006

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 62,976	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	10-FEB-2006
	05-JUL-2006
	11-JUL-2006
	13-OCT-2006 (updated stability)
	17-OCT-2006 (updated labeling)
	25-OCT-2006 (response to CMC questions)

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® (originally proposed as Rasilez®)
b) Non-Proprietary Name (USAN):	Aliskiren
c) Code Name/# (ONDC only):	SPP100
d) Chem. Type/Submission Priority:	
Chem. Type:	Type 1
Submission Priority:	S

Chemistry Review Data Sheet

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

10. PHARMACOL. CATEGORY: Renin inhibitor. Proposed for the treatment of hypertension alone and in combination with other antihypertensive agents

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150-mg and 300-mg

13. ROUTE OF ADMINISTRATION: Oral

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_____SPOTS product – Form Completed
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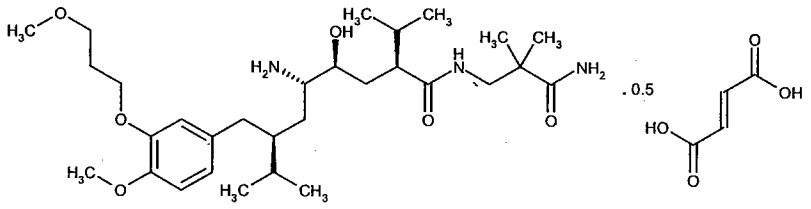
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

Chemistry Review Data Sheet

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			4	Adequate	21Oct02		
			4	Adequate	28Apr04		
			4	Adequate	07Apr05		p. 4-8 07Dec1995
			4	Adequate	09-Feb04		p. 5-10 01Apr1997
			4	Adequate	11Jul02		
			4	Adequate	16Dec03		
			4	Adequate	18Aug04		
			4	Adequate	18Mar03		

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
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18. **STATUS:**

CONSULTS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N.A.		
EES	Acceptable	08-MAR-2006	EER Summary report attached
Pharm/Tox	N.A.		
Biopharm	Adequacy of the dissolution specification Pending decision		
Labeling (OSE)	Labeling issues still under review (multi disciplinary approach)		
Methods Validation	Revalidation by Agency laboratories not recommended		
OPDRA			
EA	Satisfactory. Finding of No Significant Impact	20-MAY-2006	Bai Nguyen, Chemist, OPS, HFD-354
Microbiology	N.A.		

Chemistry Assessment
The Chemistry Review for NDA 21-985

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view his 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 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. 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)

Drug Substance

The active compound, 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 binds selectively the enzyme renin. As inhibitors of the renin-angiotensin system (RAS) have proven to be successful treatments for hypertension and renin catalyzes the rate-limiting step of RAS, rennin inhibitors are thought to be the optimal target for RAS inhibition. Aliskiren was discovered/developed employing a combination of molecular modelling and crystallographic structure analysis to design renin inhibitors lacking the extended peptide-like backbone of earlier inhibitors, for improved pharmacokinetic properties. According to the applicant, aliskiren represents the first in a novel class of renin inhibitors with the potential for treatment of hypertension and related cardiovascular diseases.

The drug substance, aliskiren hemifumarate (code name SPP100), is obtained synthetically from [redacted] starting materials previously accepted by the Agency. The manufacturing procedure is described as an [redacted]

[redacted]

Characterization studies employ conventional and well established spectroscopic techniques such as [redacted]

[redacted]

The drug substance is very soluble in aqueous media from pH 1-7.6. SPP100 does not reach a point of saturation in aqueous solutions up to 1000 g/L. The dissociation constant, pKa, of SPP100 in water at 22 °C is pKa = 9.18. The distribution coefficient of SPP100, in *n*-octanol / phosphate buffer pH = 7.4 at 22 °C is P = 10.3, $\log_{10}$ P = 1.01. It has been classified as a class 3 compound according to the Biopharmaceutics Classification System (high solubility, low permeability). [redacted]

Chemistry Assessment

Drug substance specifications include

Stability and characterization studies showed that the drug substance is sensitive to heat and humidity (very hygroscopic). In solid state, the drug substance reacts with th .o form degradation products Degradation products seen after are Stability stress studies showed that . A retest period of nder storage conditions is granted. Storage conditions require that the drug substance is , protected from light.

Drug Product

The drug product, Tekturna® (aliskiren) Tablets, is proposed to be commercialized in two dosage strengths 150-mg and 300-mg immediate release film-coated tablets for oral administration. Each 150-mg tablet contains mg of aliskiren hemifumarate (active), mg cellulose microcrystalline mg crospovidone ng Povidone ng magnesium stearate ng Colloidal Silicon Dioxide. nts include: titanium oxide, iron oxide polyethylene glyc nd hydroxypropylmethyl cellulose. All components meet compendial requirements. The two dosage strengths are prepared from the same and the core tablet composition is linear.

Through development the formulation and manufacturing process parameters were simultaneously optimized. A lower strength 75-mg was also used in clinical trials, but not proposed commercialization. The market formulations have the same formulation as the uncoated ones, except that the tablet core is film-coated with a non-functional film coat.

Drug product manufacture is described as a

In-process controls involve testing for

Drug product specifications include

Stability studies protocols include bracketing and matrix designs. Stability of the 150-mg strength tablets is inferred by bracketing of the 75-mg and 300-mg tablets. Although the 75-mg tablets are not proposed for commercialization, they were used in clinical studies. The bracketing design is fully justified as all the strengths (75-, 150- and 300-mg) are prepared from the same and the core tablet composition are the same. The coating of the three dosage strength, which is used for taste masking and coloring is slightly different (color differentiation). Based upon the use of closely related formulations in the 150-mg and 300-mg strengths a reduced matrix design is proposed for the evaluation and approval commercial package configurations which included oottles and

blisters. Stability testing program under different conditions in three types of blister packages: , blisters, and blisters was also conducted. The investigation showed that the Based on the available results, the blisters were not recommended to be marketed. Up to long-term and , accelerated stability data are presented in the original submission. Additional stability data, up to at controlled room temperature, was provided during the review. Based on the provided stability information an expiry dating of 24 months is granted under the proposed 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. Description of How the Drug Product is Intended to be Used

Aliskiren is a non-peptide renin inhibitor and is proposed for the treatment of hypertension as monotherapy or in combination with other anti-hypertensive agents. Tekturna® (Aliskiren) Tablets' are administered as an oral tablet taken once daily. The recommended starting dose is 150-mg, and for patients whose blood pressure is not adequately controlled, the daily dose can be incremented to 300-mg maximum dose. Tekturna® may be administered with other anti-hypertensive agents with or without food. Both the 150-mg and 300-mg strengths will be packaged in bottles of 30 or 90 tablets and in unit dose blister packages of 100 tablets (10 strips of 10 tablets).

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:

1. In the specifications for the starting materials
2. Your description for the drug substance reprocessing procedure ' s considered too broad. Clarify which are the specific circumstances where reprocessing could take place and the pertinent reprocessing procedure.
3. mentioned in the previous question, please provide an acceptance criterion for Assay.

Chemistry Assessment

4. Based on the test results from drug product supportive and primary stability batches, and validation batches, the acceptance criteria for and total impurities content should be tightened in accordance with process capability or a justification for their broad criteria should be provided.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Xavier Ysern, PhD	Chemist, ONDQA/ DPA I/ Branch II	Date: 27-OCT-2006
Ramesh Sood, PhD	Branch Chief, ONDQA/ DPA I/ Branch I	Date: 27-OCT-2006

C. CC Block

94 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Xavier Ysern
11/1/2006 11:19:18 AM
CHEMIST

Ramesh Sood
11/1/2006 11:30:40 AM
CHEMIST