

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-560s000

CHEMISTRY REVIEW(S)

NDA 21-560

Zortress[®] (everolimus) Tablets

Novartis Pharmaceuticals Corp.

Mark R. Seggel

ONDQA

Division of Pre-Marketing Assessment II

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1. NDA 21-560
2. REVIEW #: 6
3. REVIEW DATE: 10-MAR-2010
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Presubmission (M)	04-OCT-2002
Original (N)	19-DEC-2002
Amendment (BC) [dissolution data]	14-FEB-2003
Amendment (BC) [stability update, etc.]	01-AUG-2003
Amendment (BC) [dissolution profiles]	13-OCT-2003
Amendment (BC) [response to Pharm/Tox request for data regarding qualification of impurities]	17-OCT-2003
Amendment (BC) [response to CMC questions]	14-NOV-2003
Amendment (BC) [CMC update]	27-NOV-2007
Amendment (BC) [updated site information]	08-MAY-2008 (eCTD 0000)
Amendment (BC) [DS CMC update including revised analytical method validation]	19-MAR-2009 (eCTD 0006)
Amendment (BC) Drug product CMC update	06-DEC-2007
Amendment (BC) Drug product CMC update	30-JUN-2009 (eCTD 0010)
Amendment (BC) Drug substance CMC (editorial/formatting changes to harmonize documentation in N21-560 and N22-334)	09-SEP-2009 (eCTD 0015)
Amendment (BC) Clarification of batch numbering	11-DEC-2009

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Documents Reviewed</u>	<u>Document Date</u>
Resubmission	22-JAN-2010 (eCTD 0046)
Amendment	03-FEB-2010 (eCTD 0047)

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
East Hanover, NJ 07936-1080
Ronald G. Van Valen
Representative: Director, Drug Regulatory Affairs
862-778-7646

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: **Zortress**[®] (formerly known as Certican)
- b) Non-Proprietary Name (USAN): everolimus
- c) Code Name/#: SDZ RAD, RAD001
- d) CAS Registry Number: 159351-69-6
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 3 (Originally Type 1, but recently approved under NDA 22-334)
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); 21 CFR 314.50**10. PHARMACOL. CATEGORY: Immunosuppressant****11. DOSAGE FORM: Tablets****12. STRENGTH/POTENCY: 0.25 mg, 0.5 mg, and 0.75 mg
(1 mg strength withdrawn without prejudice to refiling)****13. ROUTE OF ADMINISTRATION: Oral****14. Rx/OTC DISPENSED: Rx OTC**

Chemistry Review Data Sheet

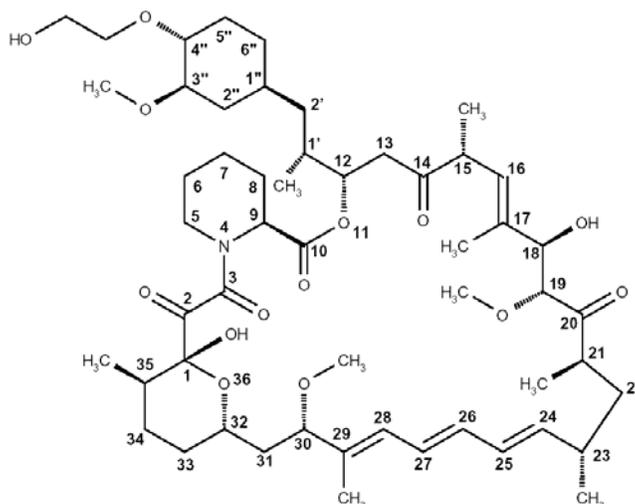
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

____ SPOTS product – Form Completed

X Not a SPOTS product

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

IUPAC: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-((1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl)-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone



IUPAC Name Numbering System

Molecular Formula: C₅₃H₈₃NO₁₄

Molecular Weight: 958.22

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15720	II	Sandoz GmbH (formerly Biochemie)	Rapamycin	1	Adequate	12/31/08 (M. Seggel)	
(b) (4)	III	(b) (4)	(b) (4)	3,4	Adequate	9/27/00 3/6/08	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Chemistry Review Data Sheet

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
IND	52,003	Commercial IND
NDA	22-334	Afinitor (everolimus) Tablets

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	12/7/09	E. Johnson, HFD-320
Pharm/Tox	Qualification of impurities acceptable	10/15/03	S. Kunder, HFD-590
Clin Pharm	Revise dissolution acceptance criterion*	10/15/03	S. Jang, HFD-590
ONDQA Biopharm	n/a		
LNC	n/a		
Methods Verification	Adequate	01-AUG-2004	N. Westenberger, St. Louis Lab.
DMEPA	Zortress™ Acceptable; <i>other labeling issues pending</i>	08-DEC-2009	J. Park, OSE/DMEPA
EA	Categorical Exclusion acceptable	-	M. Seggel
Microbiology	n/a		

*Acceptance criterion was revised as requested; see Chemistry Review #2.

The Chemistry Review for NDA 21-560

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. The package insert, and container (foil blister) and carton labeling, as revised, are acceptable from the CMC perspective. Therefore, from the CMC perspective, this NDA is recommended for approval.

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

None at this time.

II. Summary of Chemistry Assessments

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

Everolimus is a semisynthetic macrolide immunosuppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. (b) (4)

(b) (4) Everolimus is poorly water-soluble. Like sirolimus, everolimus is susceptible to oxidation. (b) (4)

(b) (4) butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an amorphous powder.

The drug product is an immediate-release compressed tablet containing everolimus in four strengths, 0.25-, 0.50, 0.75-, and 1.0-mg. {Note: Based on an administrative decision for business reasons, Novartis has withdrawn the 1 mg Tablet strength from the NDA without prejudice to refilling; see eCTD submission 0047, 2/3/2010.}

(b) (4)

Executive Summary Section

(b) (4). The quality of the tablets is assured by tests for identity, potency and purity. The drug product is packaged in unit dose blisters.

(b) (4)
The backing component is a child-resistant peel push foil (b) (4)

(b) (4) The stability of the drug product in blister packaging has been evaluated through 60 months at 25°C/60% relative humidity (RH). The product exhibits good stability under these conditions. Adequate stability was also observed at 40°C/75% RH. The proposed expiration dating period of 36 months for product stored in the proposed blister at 25°C/60% RH (excursions to 15°C and 30°C) is acceptable.

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

Everolimus is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a renal transplant. Doses of up to 3 mg everolimus per day are proposed. The product will be used in conjunction with cyclosporine and other immunosuppressants. Like other immunosuppressants, the drug product may be chronically administered to transplant recipients.

C. Basis for Approvability or Not-Approval Recommendation

Drug substance and drug product CMC has been previously reviewed (see NDA 21-560 Chemistry Reviews #1, #2, #3 and #4; also see NDA 22-334 for information regarding Afinitor (everolimus) Tablets, 5 mg and 10 mg). On the basis of Reviews #1 and #2, a recommendation for approval of NDA 21-560 from the CMC perspective was made. However, the application was not approved because of clinical deficiencies. Review #3 covered drug substance CMC in support of NDA 21-560 and NDA 22-334. Review #4 covered drug product CMC. Review #5 covers revised labeling.

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All drug substance and drug product facilities have been found acceptable. An overall site recommendation of Acceptable was issued by the Office of Compliance (07-DEC-2009; see EES).

(b) (4)
(b) (4) The acceptability of a new trademark, Zortress, and an alternative, (b) (4) were reviewed in DMEPA. 'Zortress' was found acceptable (J. Park, DMEPA, 08-DEC-2009). Labeling (package insert, blister and carton labels), as revised, are acceptable from the CMC perspective.

Executive Summary Section

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

Mark R. Seggel
{see electronic signature page}

B. Endorsement Block

Stephen P. Miller, Ph.D., Acting Branch Chief
{see electronic signature page}

C. CC Block

{see DARRTS}

5 Page(s) has been Withheld in Full immediately following this page as
B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

MARK R SEGCEL
04/15/2010

STEPHEN P MILLER
04/15/2010

NDA 21-560

Zortress[®] (everolimus) Tablets

Novartis Pharmaceuticals Corp.

Mark R. Seggel

ONDQA

Division of Pre-Marketing Assessment II

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1. NDA 21-560
2. REVIEW #: 5
3. REVIEW DATE: 17-DEC-2009
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Presubmission (M)	04-OCT-2002
Original (N)	19-DEC-2002
Amendment (BC) [dissolution data]	14-FEB-2003
Amendment (BC) [stability update, etc.]	01-AUG-2003
Amendment (BC) [dissolution profiles]	13-OCT-2003
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Amendment (BC) Drug product CMC update	30-JUN-2009 (eCTD 0010)
Amendment (BC) Drug substance CMC (editorial/formatting changes to harmonize documentation in N21-560 and N22-334)	09-SEP-2009 (eCTD 0015)
Amendment (BC) Clarification of batch numbering	11-DEC-2009

6. SUBMISSION(S) BEING REVIEWED:

Not Applicable

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
East Hanover, NJ 07936-1080
Ronald G. Van Valen
Representative: Director, Drug Regulatory Affairs
862-778-7646

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ~~Certican~~[®]; **Zortress**[®]
- b) Non-Proprietary Name (USAN): everolimus
- c) Code Name/#: SDZ RAD, RAD001
- d) CAS Registry Number: 159351-69-6
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 3 (Originally Type 1, but recently approved under NDA 22-334)
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); 21 CFR 314.50

10. PHARMACOL. CATEGORY: Immunosuppressant

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.25 mg, 0.5 mg, 0.75 mg and 1 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

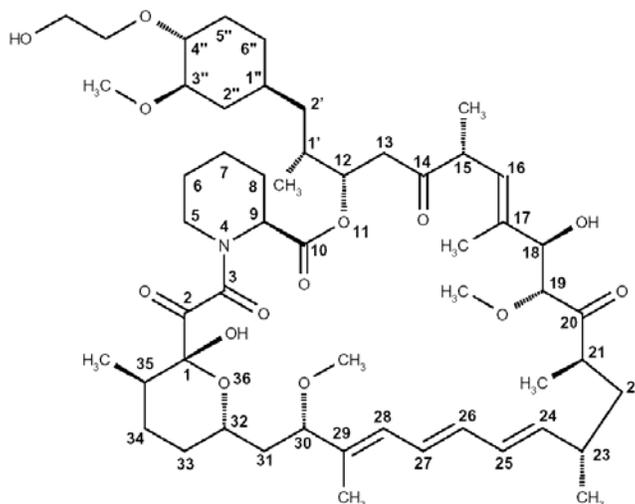
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

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IUPAC Name Numbering System

Molecular Formula: C₅₃H₈₃NO₁₄

Molecular Weight: 958.22

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

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(b)	III	(b) (4)	(b) (4)	3,4	Adequate	9/27/00 3/6/08	

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3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

Chemistry Review Data Sheet

- 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/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
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Pharm/Tox	Qualification of impurities acceptable	10/15/03	S. Kunder, HFD-590
Clin Pharm	Revise dissolution acceptance criterion*	10/15/03	S. Jang, HFD-590
ONDQA Biopharm	n/a		
LNC	n/a		
Methods Verification	Adequate	01-AUG-2004	N. Westenberger, St. Louis Lab.
DMEPA	Zortress™ Acceptable; <i>other labeling issues pending</i>	08-DEC-2009	J. Park, OSE/DMEPA
EA	Categorical Exclusion acceptable	-	M. Seggel
Microbiology	n/a		

*Acceptance criterion was revised as requested; see Chemistry Review #2.

The Chemistry Review for NDA 21-560

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues, including package insert, blister/carton labels, and REMS are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.

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

None at this time.

II. Summary of Chemistry Assessments

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

Everolimus is a semisynthetic macrolide immunosuppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. (b) (4)

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The quality of the tablets is assured by tests for identity, potency and purity. The drug product is

Executive Summary Section

packaged in unit dose blisters. (b) (4)

The backing component is a child-resistant peel push foil (b) (4) The stability of the drug product in blister packaging has been evaluated through 60 months at 25°C/60% relative humidity (RH). The product exhibits good stability under these conditions. Adequate stability was also observed at 40°C/75% RH. The proposed expiration dating period of 36 months for product stored in the proposed blister at 25°C/60% RH (excursions to 15°C and 30°C) is acceptable.

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C. Basis for Approvability or Not-Approval Recommendation

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The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All drug substance and drug product facilities have been found acceptable. An overall site recommendation of Acceptable was issued by the Office of Compliance (07-DEC-2009; see EES).

(b) (4)

(b) (4) The acceptability of a new trademark, Zortress, and an alternative, (b) (4) were reviewed in DMEPA. 'Zortress' was found acceptable (J. Park, DMEPA, 08-DEC-2009). Labeling (package insert, blister and carton labels) are under review by the review team and DMEPA. Preliminary comments have been sent to the company.

Executive Summary Section

A complete response will be issued for the application because of an inadequate/incomplete REMS (risk evaluation and mitigation strategies). Labeling negotiations will be completed during the next review cycle.

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

{see electronic signature page}

B. Endorsement Block

{see electronic signature page}

C. CC Block

{see DARRTS}

4 Page(s) has been Withheld in Full immediately following this page as
B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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

/s/

MARK R SEGCEL
12/22/2009

STEPHEN P MILLER
12/22/2009

NDA 21-560

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Novartis Pharmaceuticals Corp.

Mark R. Seggel

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6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC) Drug product CMC update	06-DEC-2007
Amendment (BC) Drug product CMC update	30-JUN-2009 (eCTD 0010)
Amendment (BC) Drug substance CMC (editorial/formatting changes to harmonize documentation in N21-560 and N22-334)	09-SEP-2009 (eCTD 0015)
Amendment (batch number assignment)	02-DEC-2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
East Hanover, NJ 07936-1080
Ronald G. Van Valen
Representative: Director, Drug Regulatory Affairs
862-778-7646

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ~~Certican~~[®]; **Zortress**[®]
- b) Non-Proprietary Name (USAN): everolimus
- c) Code Name/#: SDZ RAD, RAD001
- d) CAS Registry Number: 159351-69-6
- e) Chem. Type/Submission Priority:
 - i. Chem. Type: 3 (Originally Type 1, but recently approved under NDA 22-334)
 - ii. Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); 21 CFR 314.50

10. PHARMACOL. CATEGORY: Immunosuppressant

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.25 mg, 0.5 mg, 0.75 mg and 1 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

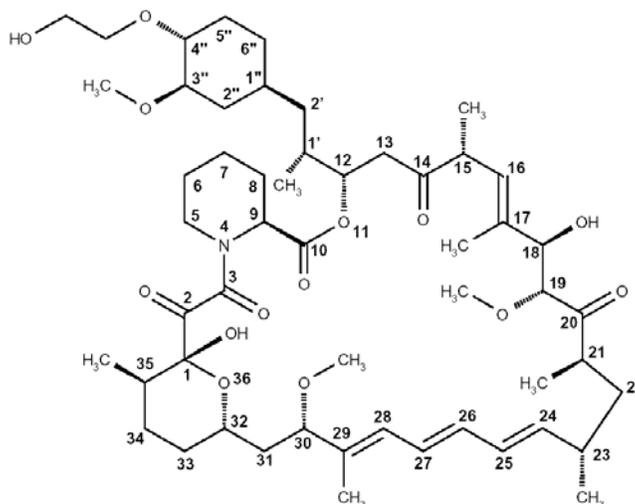
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

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

IUPAC: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone



IUPAC Name Numbering System

Molecular Formula: C₅₃H₈₃NO₁₄

Molecular Weight: 958.22

17. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15720	II	Sandoz GmbH (formerly Biochemie)	Rapamycin	1	Adequate	12/31/08	
(b)	III	(b) (4)	(b) (4)	3,4	Adequate	9/27/00 3/6/08	

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

Chemistry Review Data Sheet

- 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
IND	52,003	Commercial IND
NDA	22-334	Afinitor (everolimus) Tablets

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	<i>pending</i>		
Pharm/Tox	Qualification of impurities acceptable	10/15/03	S. Kunder, HFD-590
Clin Pharm	Revise dissolution acceptance criterion*	10/15/03	S. Jang, HFD-590
ONDQA Biopharm	n/a		
LNC	n/a		
Methods Verification	Adequate	01-AUG-2004	N. Westenberger, St. Louis Lab.
DMEPA	<i>pending</i>		
EA	Categorical Exclusion acceptable	-	M. Seggel
Microbiology	n/a		

*Acceptance criterion was revised as requested; see Chemistry Review #2.

The Chemistry Review for NDA 21-560

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

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

None at this time.

II. Summary of Chemistry Assessments

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

Everolimus is a semisynthetic macrolide immunosuppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. (b) (4)

(b) (4). Everolimus is poorly water-soluble. Like sirolimus, everolimus is susceptible to oxidation. (b) (4)

(b) (4) butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an amorphous powder.

The drug product is an immediate-release compressed tablet containing everolimus in four strengths, 0.25-, 0.50, 0.75-, and 1.0-mg. (b) (4)

(b) (4) The quality of the tablets is assured by tests for identity, potency and purity. The drug product is packaged in unit dose blisters. (b) (4)

Executive Summary Section

(b) (4) The backing component is a child-resistant peel push foil (b) (4) The stability of the drug product in blister packaging has been evaluated through 60 months at 25°C/60% relative humidity (RH). The product exhibits good stability under these conditions. Adequate stability was also observed at 40°C/75% RH. The proposed expiration dating period of 36 months for product stored in the proposed blister at 25°C/60% RH (excursions to 15°C and 30°C) is acceptable.

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

Everolimus is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a renal transplant. Doses of up to 3 mg everolimus per day are proposed. The product will be used in conjunction with cyclosporine and other immunosuppressants. Like other immunosuppressants, the drug product may be chronically administered to transplant recipients.

C. Basis for Approvability or Not-Approval Recommendation

Drug substance and drug product CMC has been previously reviewed (see NDA 21-560 Chemistry Reviews #1, #2 and #3; also see NDA 22-334 for information regarding Afinitor (everolimus) Tablets, 5 mg and 10 mg). On the basis of Reviews #1 and #2, a recommendation for approval of NDA 21-560 from the CMC perspective was made. However, the application was not approved because of clinical deficiencies. Review #3 covered drug substance CMC in support of NDA 21-560 and NDA 22-334.

Two drug product CMC amendments (06-DEC-2007 and 30-JUN-2009) are the subject of this review. The most significant change reported is the tightening of acceptance criteria in the drug product specification.

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

Labeling issues are still pending. (b) (4)

(b) (4) The acceptability of a new trademark, Zortress, and alternative (b) (4), are under review in DMEPA.

At this time, one facility in Switzerland is assigned for a cGMP inspection. All other drug substance and drug product facilities have been found acceptable. An overall site recommendation from the Office of Compliance has not been made.

Executive Summary Section

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

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B. Endorsement Block

{see electronic signature page}

C. CC Block

{see DARRTS}

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

MARK R SEGCEL
12/03/2009

STEPHEN P MILLER
12/03/2009

NDA 21-560
NDA 22-334*

Certican[®] (everolimus) Tablets
***Afinitor[®] (everolimus) Tablets**

Novartis Pharmaceuticals Corp.

Mark R. Seggel
ONDQA
Division of Pre-Marketing Assessment II

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Chemistry Review Data Sheet

1. NDA: **21-560** and **22-334** (and associated NDAs 21-628, 21-561, 21-631)
2. REVIEW #: 3 [of NDA 21-560] (Covering Drug Substance CMC Only)
3. REVIEW DATE: March 4, 2009
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Presubmission (M)	04-OCT-2002
Original (N)	19-DEC-2002
Amendment (BC) [dissolution data]	14-FEB-2003
Amendment (BC) [stability update, etc.]	01-AUG-2003
Amendment (BC) [dissolution profiles]	13-OCT-2003
Amendment (BC) [response to Pharm/Tox request for data regarding qualification of impurities]	17-OCT-2003
Amendment (BC) [response to CMC questions]	14-NOV-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC) [CMC update]	27-NOV-2007
Amendment (BC) [updated site information]	08-MAY-2008
Amendment (BC) [revised analytical method validation] (submitted to N22-334)	20-JAN-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Chemistry Review Data Sheet

Address: One Health Plaza
East Hanover, NJ 07936-1080
Representative: Ronald G. Van Valen
(NDA 21-560): Director, Drug Regulatory Affairs
862-778-7646

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Certican[®] / Afinitor[®]
- b) Non-Proprietary Name (USAN): everolimus
- c) Code Name/#: SDZ RAD, RAD001
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: -

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); 21 CFR 314.50

10. PHARMACOL. CATEGORY: Immunosuppressant; anticancer agent

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY:

NDA 21-560/21-628: 0.25 mg, 0.50 mg, 0.75 mg and 1.00 mg
NDA 22-334: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet

Everolimus:

IUPAC: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

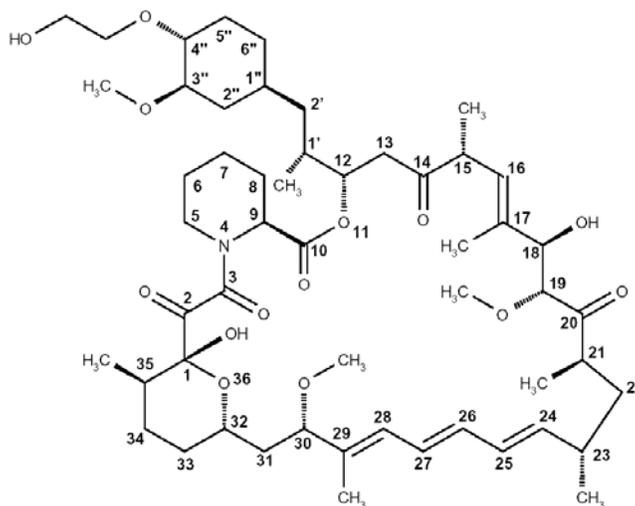


Figure 1. IUPAC Name Numbering System

CAS: 42-O-(2-hydroxyethyl)-rapamycin (9CI)

CAS registry #: 159351-69-6

Research Codes: RAD; SDZ RAD; RAD001; RAD 666; RAD 001-NXB; RAD n BHT

Other Names: 40-O-(2-hydroxyethyl)-rapamycin; 4''-O-(2-hydroxyethyl)-rapamycin

Note: At least two other numbering systems have been used for this class of macrolides. The numbering system used in the CAS name is based on the numbering system used in the original American Home Products patent. The Novartis system, also widely used by academia and in scientific publications, uses the lactone carbonyl group as the starting point (see Figure 2).

Chemistry Review Data Sheet

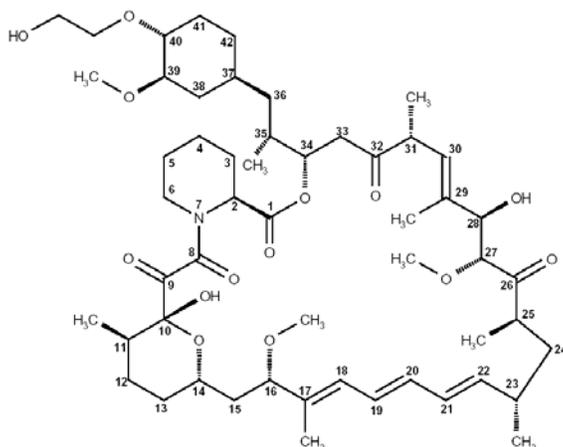


Figure 2. Numbering System Used by Novartis

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15720	II	Sandoz GmbH (formerly Biochemie)	Rapamycin	1	Adequate	12/31/08	
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate		

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
IND	52,003	Commercial IND

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Pharm/Tox	Qualification of impurities in Certican [®] acceptable	10/15/03	S. Kunder
EES	Acceptable	2/23/09	S. Adams, HFD-325

Executive Summary Section

The Chemistry Review for NDA 21-560, etc.

(Drug Substance Only)

The Executive Summary

Everolimus is the active ingredient in several Novartis applications. All use the same everolimus
(b) (4)

Reference Number	Indication	Status
NDA 21-560	Certican [®] Tablets; Prophylaxis of organ rejection in allogeneic renal transplant recipients	AE 20-OCT-2003 AE 27-AUG-2004 (for Clinical)
NDA 21-628	Certican [®] Tablets; Prophylaxis of organ rejection in allogeneic heart transplant recipients	AE 20-OCT-2003 AE 27-AUG-2004 (for Clinical)
NDA 21-561	Certican [®] Tablets for Oral Suspension; Prophylaxis of organ rejection in allogeneic renal transplant recipients	AE 03-DEC-2003
NDA 21-631	Certican [®] Tablets for Oral Suspension; Prophylaxis of organ rejection in allogeneic heart transplant recipients	AE 03-DEC-2003
NDA 22-334	Afinitor [®] Tablets; Treatment of advanced renal cell carcinoma	Under review in DDOP/OODP

I. Recommendations

A. Recommendation and Conclusion on Approvability

This review only covers drug substance CMC as recently amended.

Sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance, everolimus. The drug substance manufacturing facilities have acceptable cGMP status. From the chemistry, manufacturing and controls perspective, applications making reference to everolimus drug substance CMC in NDA 21-560 can be approved. The adequacy of drug product CMC is being evaluated under separate NDA reviews.

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

None at this time.

Executive Summary Section

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

Certican Tablets and Afinitor Tablets contain everolimus, a semisynthetic macrolide immuno-suppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. (b) (4)

Everolimus is poorly water-soluble. Like sirolimus, everolimus is susceptible to oxidation. (b) (4)

butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an amorphous powder.

See NDA specific drug product reviews (NDA 21-560 Chemistry Reviews #1, #2 and future review; NDA 22-334 Chemistry Reviews) for comments on the drug products.

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

Doses of up to 3 mg everolimus per day are proposed for use in transplantation. The product will be used in conjunction with cyclosporine and other immunosuppressants. Like other immunosuppressants, the drug product could be administered chronically to transplant recipients.

Tablets containing 5- and 10-mg of everolimus will be available for treatment of renal cell carcinoma. A 10 mg once daily, for as long as clinical benefit is observed or until unacceptable toxicity occurs, is proposed. A dose reduction to 5 mg per day due to severe side effects or in the case of moderate hepatic impairment is also proposed.

C. Basis for Approvability or Not-Approval Recommendation

At the time of the original FDA action (AE, 20-OCT-2003) the primary outstanding CMC issue related to the manufacture of sirolimus, an intermediate in the manufacture of everolimus. The DMF covering the manufacture of sirolimus by Biochemie G.m.b.H. (now dba Sandoz) was initially found deficient (see Chemistry Review #1 for DMF 15720). The response was not received in time for a thorough review during the first review cycle. The response was subsequently reviewed and found acceptable (see Chemistry Review #2 for DMF

Executive Summary Section

15720). An update to DMF 15720 was recently reviewed and found adequate (see Chemistry Review #3 for DMF 15720).

During the first review cycle a number of issues, most minor and all considered not approvability issues, were communicated to the applicant. The responses to these issues were covered in Chemistry Review #2. All responses were adequate.

The 17-OCT-2003 amendment was a formal response to Pharm/Tox request for data regarding qualification of impurities. The data were available to the reviewer prior to the formal submission of this amendment and had been considered prior to the 20-OCT-2003 action. For qualification of impurities in the higher strength Afinitor Tablets, see Chemistry Reviews for NDA 22-334.

Minor modifications to the drug substance manufacturing process were reported in BC -27-NOV-2007.

The facilities previously had been found to have acceptable cGMP status in conjunction with NDA 21-560 (see Chemistry Review #1). The cGMP status of the facilities is currently being determined in conjunction with NDA 22-334. A recent inspection of Novartis Pharma AG, Basel, identified a deficiency in the validation of HPLC Method 30001.01, Determination of Related Substances in the Drug Substance. Apparently the method was not completely validated with respect to the determination of (b) (4). A revised validation report was submitted to NDA 22-334 on January 20, 2009. As a result, the proposed structure of (b) (4) has been revised and a new (b) (4) established. Previous testing may have slightly overestimated the amount of (b) (4) actually present. The acceptance criterion for (b) (4) has been tightened from NMT (b) (4) to NMT (b) (4).

Additional long-term stability data have been collected at -20°C and 5°C. The results support the proposed retest period of 60-months for drug substance stored at 2-8°C.

Note that, from the clinical perspective, NDA 21-560 and NDA 21-628 are not recommended for approval. The applicant has not adequately addressed the clinical issues identified in the 20-OCT-2003 Approvable Letter. While the drug appears to be efficacious, a 'safe' dosing regimen remains to be established.

Executive Summary Section

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

{see appended electronic signature page}

B. Endorsement Block

{see appended electronic signature page}

C. CC Block

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/s/

Mark Seggel
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Norman Schmuff
3/5/2009 08:43:02 AM
CHEMIST

NDA 21-560
NDA 21-628

Certican[®] (everolimus) Tablets

Novartis Pharmaceuticals Corp.

Mark R. Seggel
Division of Special Pathogen and
Immunologic Drug Products

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Chemistry Review Data Sheet

1. NDA 21-560 and NDA 21-628

2. REVIEW #: 2

3. REVIEW DATE: July 26, 2004

4. REVIEWER: Mark R. Seggel

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Presubmission (M)	04-OCT-2002
Original (N)	19-DEC-2002
Amendment (BC) [dissolution data]	14-FEB-2003
Amendment (BC) [stability update, etc.]	01-AUG-2003
Amendment (BC) [dissolution profiles]	13-OCT-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (BC) [response to Pharm/Tox request for data regarding qualification of impurities]	17-OCT-2003
Amendment (BC) [response to CMC questions]	14-NOV-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation
Address: One Health Plaza
East Hanover, NJ 07936-1080

Chemistry Review Data Sheet

Representative: Ronald G. Van Valen
Director, Drug Regulatory Affairs
862-778-7646
Robert J. Clark
CMC Contact: Director, Global Regulatory CMC
862-778-7005

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Certican®
- b) Non-Proprietary Name (USAN): everolimus
- c) Code Name/# (ONDC only): SDZ RAD, RAD001
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); 21 CFR 314.50

10. PHARMACOL. CATEGORY: Immunosuppressant

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.25 mg, 0.50 mg, 0.75 mg and 1.00 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet

Everolimus:

IUPAC: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

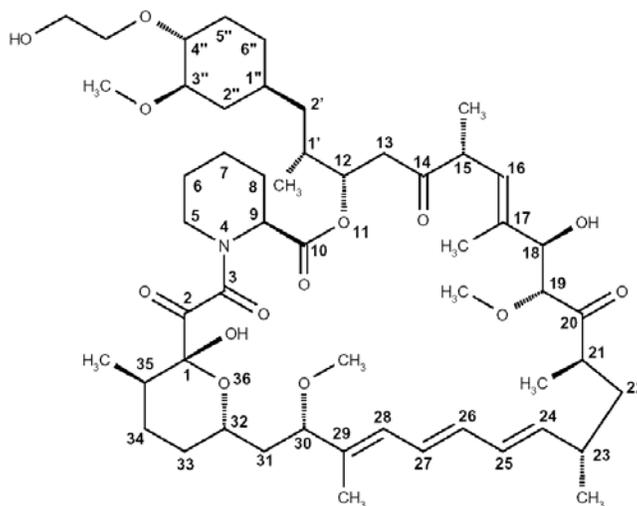


Figure1. IUPAC Name Numbering System

CAS: 42-O-(2-hydroxyethyl)-rapamycin (9CI)

CAS registry #: 159351-69-6

Research Codes: RAD; SDZ RAD; RAD001; RAD 666; RAD 001-NXB; RAD n BHT

Other Names: 40-O-(2-hydroxyethyl)-rapamycin; 4''-O-(2-hydroxyethyl)-rapamycin

Note: At least two other numbering systems have been used for this class of macrolides. The numbering system used in the CAS name is based on the numbering system used in the original American Home Products patent. The Novartis system, also widely used by academia and in scientific publications, uses the lactone carbonyl group as the starting point (see Figure 2).

Chemistry Review Data Sheet

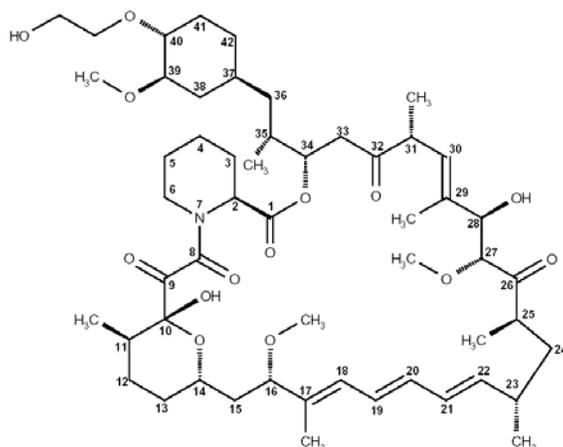


Figure 2. Numbering System Used by Novartis

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15720	II	Biochemie GmbH (now Sandoz)	Rapamycin	1	Adequate	11/03/03	As amended
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate		

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
IND	52,003	Commercial IND

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		
EES	Acceptable	10/6/03	J. D. Ambrogio
Pharm/Tox	Qualification of impurities acceptable	10/15/03	S. Kunder
Biopharm	Revise dissolution acceptance criterion	10/15/03	S. Jang
LNC	n/a		
Methods Validation	submitted	pending	
ODS/DMETS	(b) (4)	10/9/03	S. Dallas
EA	Claim for categorical exclusion is acceptable	-	M. Seggel
Microbiology	n/a		

Executive Summary Section

The Chemistry Review for NDAs 21-560 and 21-628

The Executive Summary

Administrative Note: For administrative purposes, NDA numbers as listed below were assigned to each of the proposed indications originally submitted in NDA 21-560. Once a final action is taken on NDA 21-628, the NDA number will be retired and all future correspondence will refer to NDA 21-560.

Reference Number	Indication
NDA 21-560	Prophylaxis of organ rejection in allogeneic renal transplant recipients
NDA 21-628	Prophylaxis of organ rejection in allogeneic heart transplant recipients

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective, an Approval action is recommended for these New Drug Applications. The major deficiency relating to the manufacture of sirolimus, an intermediate in the manufacture of everolimus, as described in DMF 15720, has been adequately resolved.

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

None at this time.

II. Summary of Chemistry Assessments

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

Certican Tablets contain everolimus, a semisynthetic macrolide immunosuppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. (b) (4)

Everolimus is poorly water-soluble. Like sirolimus, everolimus is very susceptible to oxidation. (b) (4)

Executive Summary Section

(b) (4) butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an amorphous powder. Product quality is assured by tests for identity, potency and purity.

The drug product is an immediate-release compressed tablet containing everolimus in 4 strengths, 0.25-, 0.50, 0.75-, and 1.0-mg. (b) (4)

The quality of the tablets is assured by tests for identity, potency and purity. The drug product is packaged in unit dose blisters. (b) (4)

The backing component is a child-resistant peel push foil (b) (4)
(b) (4) The stability of the drug product in blister packaging has been evaluated through 36 months at 25°C/60% relative humidity (RH). The product exhibits good stability under these conditions. Adequate stability was also observed at 40°C/75% RH. The proposed expiration dating period of 36 months for product stored in the proposed blister at 25°C/60% RH (excursions to 15°C and 30°C) is acceptable.

(b) (4)

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

Doses of up to 3 mg everolimus per day are proposed. The product will be used in conjunction with cyclosporine and other immunosuppressants. Like other immunosuppressants, the drug product could be administered chronically to transplant recipients.

C. Basis for Approvability or Not-Approval Recommendation

At the time of the original FDA action (AE, 20-OCT-2003) the primary outstanding CMC issue related to the manufacture of sirolimus, an intermediate in the manufacture of everolimus. The DMF covering the manufacture of sirolimus by Biochemie G.m.b.H. was initially found deficient (see Chemistry Review #1 for DMF 15720). The response was not received in time for a thorough review during the first review cycle. The response was subsequently reviewed and found acceptable (see Chemistry Review #2 for DMF 15720).

Executive Summary Section

During the first review cycle a number of issues, most minor and all considered not approvability issues, were communicated to the applicant. The responses to these issues are covered in this review. All responses were adequate.

The 17-OCT-2003 amendment was a formal response to Pharm/Tox request for data regarding qualification of impurities. The data were available to the reviewer prior to the formal submission of this amendment and had been considered prior to the 20-OCT-2003 action.

The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.

Note that, from the clinical perspective, NDA 21-560 and NDA 21-628 remain approvable. The applicant has not adequately addressed the clinical issues identified in the 20-OCT-2003 Approvable Letter. While the drug appears to be efficacious, a 'safe' dosing regimen remains to be established.

III. Administrative

A. Reviewer's Signature

{see appended electronic signature page}

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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

/s/

Mark Seggel
8/19/04 11:45:37 AM
CHEMIST
N21-560 Chem. Rev. #2

Norman Schmuft
8/20/04 04:11:25 PM
CHEMIST

NDA 21-560

NDA 21-628

Certican[®] (everolimus) Tablets

Novartis Pharmaceuticals Corp.

**Mark R. Seggel
Division of Special Pathogen and
Immunologic Drug Products**

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Chemistry Review Data Sheet

1. NDA 21-560 and NDA 21-628
2. REVIEW #: 1
3. REVIEW DATE: October 20, 2003
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

Previous Documents

not applicable

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Presubmission (M)

Original (N)

Amendment (BC) [dissolution data]

Amendment (BC) [stability update, etc.]

Amendment (BC) [dissolution profiles]

Document Date

04-OCT-2002

19-DEC-2002

14-FEB-2003

01-AUG-2003

13-OCT-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Address: One Health Plaza
East Hanover, NJ 07936-1080

Chemistry Review Data Sheet

Representative: Ronald G. Van Valen
Director, Drug Regulatory Affairs
862-778-7646
Robert J. Clark
CMC Contact: Director, Global Regulatory CMC
862-778-7005

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Certican®
- b) Non-Proprietary Name (USAN): everolimus
- c) Code Name/# (ONDC only): SDZ RAD, RAD001
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1); 21 CFR 314.50

10. PHARMACOL. CATEGORY: Immunosuppressant

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 0.25 mg, 0.50 mg, 0.75 mg and 1.00 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

Chemistry Review Data Sheet

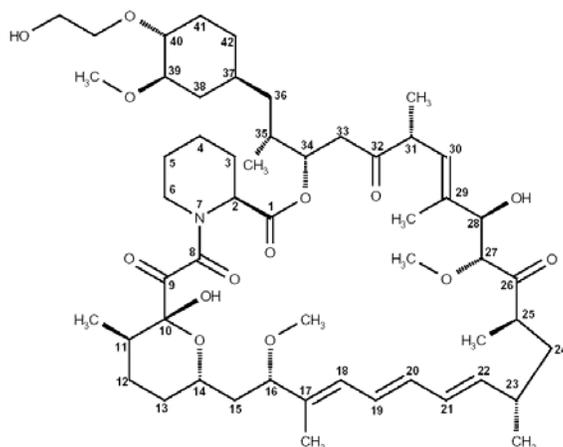


Figure 2. Numbering System Used by Novartis

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15720	II	Biochemie GmbH (now Sandoz)	Rapamycin	1	Inadequate	8/20/03	Major deficiencies noted
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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5 – Authority to reference not granted

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Chemistry Review Data Sheet

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Biopharm	Revise dissolution acceptance criterion	10/15/03	S. Jang
LNC	n/a		
Methods Validation	submitted	pending	
ODS/DMETS	(b) (4)	10/9/03	S. Dallas
EA	Claim for categorical exclusion is acceptable	-	M. Seggel
Microbiology	n/a		

Executive Summary Section

The Chemistry Review for NDAs 21-560 and 21-628

The Executive Summary

Administrative Note: For administrative purposes, NDA numbers as listed below were assigned to each of the proposed indications originally submitted in NDA 21-560. Once a final action is taken on NDA 21-628, the NDA number will be retired and all future correspondence will refer to NDA 21-560.

Reference Number	Indication
NDA 21-560	Prophylaxis of organ rejection in allogeneic renal transplant recipients
NDA 21-628	Prophylaxis of organ rejection in allogeneic heart transplant recipients

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective at this time, an Approvable action is recommended for these New Drug Applications. The major remaining deficiency relates to the manufacture of sirolimus, an intermediate in the manufacture of everolimus, as described in DMF 15720.

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

None at this time.

II. Summary of Chemistry Assessments

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

Certican Tablets contain everolimus, a semisynthetic macrolide immunosuppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. (b) (4)

Everolimus is poorly water-soluble. Like sirolimus, everolimus is very susceptible to oxidation. (b) (4)

Executive Summary Section

(b) (4) butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an amorphous powder. Product quality is assured by tests for identity, potency and purity.

The drug product is an immediate-release compressed tablet containing everolimus in 4 strengths, 0.25-, 0.50, 0.75-, and 1.0-mg. (b) (4)

The quality of the tablets is assured by tests for identity, potency and purity. The drug product is packaged in unit dose blisters. (b) (4)

The backing component is a child-resistant peel push foil (b) (4)
(b) (4) The stability of the drug product in blister packaging has been evaluated through 36 months at 25°C/60% relative humidity (RH). The product exhibits good stability under these conditions. Adequate stability was also observed at 40°C/75% RH. The proposed expiration dating period of 36 months for product stored in the proposed blister at 25°C/60% RH (excursions to 15°C and 30°C) is acceptable.

(b) (4)

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

Doses of up to 3 mg everolimus per day are proposed. The product will be used in conjunction with cyclosporine and other immunosuppressants. Like other immunosuppressants, the drug product could be administered chronically to transplant recipients.

C. Basis for Approvability or Not-Approval Recommendation

At this time, the primary outstanding CMC issue relates to the manufacture of sirolimus, an intermediate in the manufacture of everolimus. The DMF covering the manufacture of sirolimus by Biochemie G.m.b.H. was previously found deficient (see Chemistry Review #1 for DMF 15720). The response was not received in time for a thorough review during this review cycle.

The applicant has responded to our request for dissolution profiles. Based on this information, we have proposed a tighter acceptance criterion. In response to

Executive Summary Section

another request, additional information has been provided to the reviewing toxicologist regarding qualification of impurities.

There appear to be a several cases where the specifications for both drug substance and drug product can be tightened. For example, the acceptance criteria (b) (4)

We have requested a commitment from Novartis to re-evaluate the acceptance criteria after additional experience with the drug substance and drug product is gained. There are a number of other relatively minor issues that require clarification or explanation, and have been communicated with the applicant. For example, the applicant has been asked to verify that the drug substance contain/closure system is in compliance with 21 CFR 177. We do not consider the aforementioned issues as approvability issues. A commitment from Novartis to address these issues in a timely manner is acceptable at this time.

The manufacturing and testing facilities have acceptable cGMP status and the Office of Compliance has issued an Overall Recommendation of Acceptable for the NDA.

Note that, from the clinical perspective, NDA 21-560 and NDA 21-628 are approvable. While the drug appears to be efficacious, a 'safe' dosing regimen has not been established.

III. Administrative

A. Reviewer's Signature

{see appended electronic signature page}

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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Mark Seggel
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CHEMIST
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Norman Schmuiff
10/20/03 08:16:54 PM
CHEMIST