

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-334**

**CHEMISTRY REVIEW(S)**

ONDQA Division Director's Memo  
NDA 22-334, AFINITOR (everolimus) Tablets 5 mg and 10 mg  
Date: 25-MAR-2009

## Introduction

AFINITOR brand of (everolimus) is a kinase inhibitor used to treat advanced renal cell carcinoma.

The shelf life of the 5 mg and 10 mg oral tablet drug products are twenty-four (24) months at controlled room temperature (also label to protect from light and moisture). This information needs to be included in the action letter.

## Administrative

The original submission of this 505(b)(1) NDA was received 27-JUN-2008 from Novartis Pharmaceuticals. **This NDA was reviewed as a priority application.** A total of twelve (12) **amendments were reviewed** in addition to the original submission; these 12 amendments spanned 29-AUG-2008 through 11-MAR-2009.

Several INDs and NDAs are associated with AFINITOR. These include I66279 (oncology), \_\_\_\_\_ (transplant), \_\_\_\_\_ (kidney transplant, submitted, not approved), and N21628 (heart transplant, submitted, not approved).

b(4)

All consults are acceptable. These include EES (overall acceptable as of 23-FEB-2009) and OSE/DMEPA 11-AUG-2008.

There are no outstanding CMC deficiencies or agreements for the approval of the 5 mg and 10 mg strengths. However, the Medical Division has asked the applicant to develop (as a post marketing commitment) a new 2.5 mg strength.

**ONDQA recommends approval (AP) of the 5 mg and 10 mg tablet strengths as provided in the original submission and as provided in the twelve amendments cited herein.**

**Drug Substance (everolimus):**  $C_{53}H_{83}NO_{14}$  and the molecular weight is 958.22.

Everolimus (USAN) drug substance, is chemically described (IUPAC) as (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-dioxo-4-azatricyclo[30.3.1.04,9]-hexatriaconta- 16,24,26,28-tetraene-2,3,10,14,20-pentaone. Everolimus (a.k.a., 40-O-(2-hydroxyethyl)-rapamycin) is a semi-synthetic substance derived from serolimus (a.k.a., rapamycin) which is obtained via fermentation (*Streptomyces hygroscopicus*).

Everolimus is produced \_\_\_\_\_

Everolimus is \_\_\_\_\_ soluble, susceptible to \_\_\_\_\_, and photodegradation.

b(4)

### **Drug Product (AFINITOR) Tablets 5 mg and 10 mg**

Both strengths of AFINITOR tablets are **immediate release (IR)**. For stability reasons, everolimus drug substance is \_\_\_\_\_ BHT during drug product manufacture. The tablets are \_\_\_\_\_ formulated and contain lactose, crospovidone, and magnesium stearate as excipients. Both strengths utilize the same blend (i.e., proportionally formulated); the 5 mg tablets weight \_\_\_\_\_ g each and the 10 mg tablets weight \_\_\_\_\_ g each.

b(4)

The drug product is **packaged in blisters** which contain aluminum foil layers in the laminate on both sides of the blister. The shelf life of the 5 mg and 10 mg oral tablet drug products in this package configuration is twenty-four (24) months at controlled room temperature (also label to protect from light and moisture). This information needs to be included in the action letter.

Rik Lostritto, Ph.D., Director, ONDQA Division III

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/s/

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Richard Lostritto  
3/26/2009 02:07:37 PM  
CHEMIST



**NDA 22-334**

**Afinitor<sup>®</sup>  
(everolimus) tablets**

**Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080**

**Ravindra K. Kasliwal, Ph.D.  
CMC Reviewer  
Division of Pre-marketing Assessment and  
Manufacturing Science,  
Branch V, ONDQA  
CDER, FDA**

**For The Division of Drug Oncology Products**



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# Chemistry Review Data Sheet

1. NDA 22-334
2. REVIEW #: 1
3. REVIEW DATE: 17-Mar-2009
4. REVIEWER: Ravindra K Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original	27-Jun-2008
Amendment (BC)	29-Aug-2008
Amendment (BC)	05-Sep-2008
Amendment (BC)	09-Sep-2008
Amendment (BC)	29-Sep-2008
Amendment (BC)	31-Oct-2008
Amendment (BL)	12-Jan-2009
Amendment (BC)	20-Jan-2009
Amendment (BC)	17-Feb-2009
Amendment (BZ)	23-Feb-2009
Amendment (BL)	27-Feb-2009
Amendment (BM)	03-Mar-2009
Amendment (BC)	11-Mar-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation  
Address: One Health Plaza  
East Hanover, NJ 07936 - 1080  
Representative: Sibylle Jennings, Ph.D.  
Associate Director, Regulatory Affairs  
Telephone: (862) 778 - 1196

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Afinitor<sup>®</sup>
- b) Non-Proprietary Name (USAN): everolimus
- c) Code Name/# (ONDC only): RAD 001

Chemistry Review Data Sheet

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: Kinase inhibitor

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

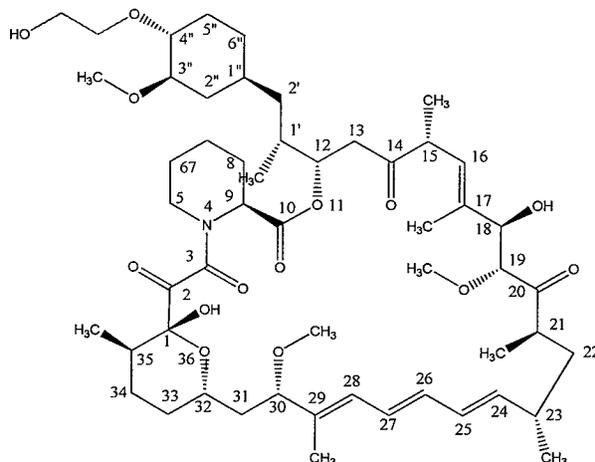
14. Rx/OTC DISPENSED:   X   Rx        OTC

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

       SPOTS product – Form Completed

  X   Not a SPOTS product

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



Chemical Formula: C<sub>53</sub>H<sub>83</sub>NO<sub>14</sub>  
Molecular Weight: 958.22  
Elemental Analysis: C, 66.43; H, 8.73; N, 1.46; O, 23.38

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

DMF	TY- PE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	III			7	Adequate	n/a	The materials meet the requirements of 21 CFR Sections 174-186 for use in direct or indirect contact with food. DMF not reviewed as per the ONDC policy statement of 29-May-2002.
15720	II	Sandoz GmbH (formerly Biochemie)	Rapamycin	1	Adequate	31-Dec-08	Review was performed by Dr. Mark R. Seggel

<sup>1</sup> 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")

<sup>2</sup> 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	66, 279	Commercial IND to study oncologic indication.
IND		Commercial IND to study transplant indication.
NDA		Sponsor's NDA for same drug substance and similar drug product (different strengths) submitted (not approved) for renal transplant indication.
NDA	21-628	Sponsor's NDA for same drug substance and similar drug product (different strengths) submitted (not approved) for heart transplant indication.

### 18. STATUS:

#### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	n/a		-
EES	Acceptable	23-Feb-2009	S. Adams
Pharm/Tox	Qualification of drug product impurities is acceptable.	26-Jan-2009	Shwu-Luan Lee, Ph.D.
Biopharm	n/a		-
LNC	n/a		-
Methods Validation	Analytical methods are conventional, DPA verification will not be requested.	-	-
OSE/DMETS	Proposed trademark, A finitor is acceptable.	11-Aug-2008	Melina Griffis, R.Ph.,
EA	Claim for categorical exclusion is acceptable	-	Ravindra K. Kasliwal, Ph.D.
Microbiology	n/a		-



Chemistry Assessment Section

# The Chemistry Review for NDA 22-334

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability:

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) under section 505 of the Act.

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

In order to achieve proper dose reductions the following post marketing commitment was agreed to by Novartis in their submission dated 03-Mar-2009:

Develop and propose a 2.5 mg dosing form (tablet) to allow for proper dose reductions when everolimus needs to be co-administered with moderate CYP3A4 inhibitors. The 2.5 mg dose form should be sufficiently distinguishable from the 5 mg and the 10 mg tablets. Full chemistry, manufacturing and controls (CMC) information for the 2.5 mg dosage form including the batch data and stability data, labels, updated labeling; updated environmental assessment section is required in a prior approval supplement.

*Protocol submission Date:* 45 days from date of action.

*Submission Date:* 6 months after FDA agreement to submitted protocol

### II. Summary of Chemistry Assessments

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

The Afinitor tablets are an immediate release dosage form for oral administration containing 5 mg and 10 mg everolimus drug substance (tablet weights are 250 mg and 500mg, respectively). The 5 mg and 10 mg tablet are white to slightly yellowish, elongated tablets with beveled edges and no scoring. The 5 mg and 10 mg tablet are sufficiently distinguishable due to their different dimensions and their different debossment.

Afinitor tablet contains everolimus drug substance, which is chemically described as (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-dioxo-4-azatricyclo[30.3.1.04,9]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone (IUPAC). It is a semisynthetic macrolide derived from sirolimus, also known as Rapamycin. Rapamycin 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. Everolimus, or 40-O-(2-hydroxyethyl)-rapamycin, is obtained

b(4)

Everolimus is \_\_\_\_\_ soluble, \_\_\_\_\_ and is amenable to photodegradation. Because of the \_\_\_\_\_ butylated hydroxytoluene (BHT), a commonly used antioxidant for the manufacture of Afinitor tablets. The everolimus in combination with BHT (referred to as RAD N BHT) is \_\_\_\_\_

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## Chemistry Assessment Section

b(4)

The stability of the drug product in blister packaging has been evaluated through 24 months at 25°C/60% relative humidity (RH) and at 30°C/75% RH. The product exhibits good stability under these conditions. Adequate stability was also observed at 40°C/75% RH. Analysis of the data supports a 24 months expiration dating period when stored in \_\_\_\_\_ aluminum blisters \_\_\_\_\_ at 25°C/60% RH and 30°C/75% RH (long-term storage condition). Additionally, it has been shown that everolimus is light sensitive, so Afinitor tablets need to be protected from light. Following storage statement is recommended: "Store at 25 °C (77 °F); excursions permitted to 15 – 30 °C (59 – 86 °F); protect from light and moisture". An expiration dating period of 24-months is granted.

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

Afinitor is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma after disease progression following treatment with sunitinib, sorafenib, \_\_\_\_\_. A dose of 10 mg once daily is recommended. \_\_\_\_\_ However, the dose may be reduced to 5 mg or increased to 20 mg in certain individuals. The drug may be administered as long as clinical benefit is observed or until unacceptable toxicity occurs.

b(4)

**C. Basis for Approvability or Not-Approval Recommendation**

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) based on the following:

- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance, everolimus (See review dated 04-Mar-2009, by Mark R. Seggel, CMC reviewer, ONDQA).
- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
- The Drug Master File #15720 (Sandoz GmbH, formerly Biochemie, for Rapamycin Manufacture) is adequate (See review dated 08-Dec-2008 by Mark R. Seggel, CMC reviewer, ONDQA)
- While the Drug Master Files \_\_\_\_\_, was not reviewed as per the ONDC policy statement of 29-May-2002, the blister backing foil \_\_\_\_\_ materials meet the requirements of 21 CFR Sections 174-186 for use in direct or indirect contact with food.
- The Office of Compliance has recommended that the drug substance and drug product manufacturing facilities are acceptable as of 23-Feb-2009 (see appendix 2).
- Issues related to carton and container labels have been adequately resolved.
- The proposed trademark, Afinitor has been found to be acceptable by OSE.

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### **III. Administrative**

#### **A. Reviewer's Signature**

*Ravindra K. Kasliwal, Ph.D.*

#### **B. Endorsement Block**

Chemist Name / Date: Ravindra K. Kasliwal, Ph.D./ date – see DFS

Chemistry Branch Chief Name / Date: Sarah C. Pope, Ph.D. / date – See DFS

Project Manager Name / Date: Christy L. Cottrell / date – See DFS

#### **C. CC Block**

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Ravi Kasliwal  
3/17/2009 08:06:07 AM  
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Sarah Pope  
3/18/2009 11:35:17 AM  
CHEMIST





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# Chemistry Review Data Sheet

1. NDA: ——— 22-334 (and associated NDAs 21-628, ———

b(4)

2. REVIEW #: 3 [of NDA ——— (Covering Drug Substance CMC Only)

b(4)

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 #3



## Chemistry Review Data Sheet

Address: One Health Plaza  
East Hanover, NJ 07936-1080  
Representative: Ronald G. Van Valen  
(NDA           ) Director, Drug Regulatory Affairs **b(4)**  
           862-778-7646

### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:            / Afinitor® **b(4)**
- 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            21-628: 0.25 mg, 0.50 mg, 0.75 mg and 1.00 mg **b(4)**  
NDA 22-334: 5 mg and 10 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:

## 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<sup>4,9</sup>]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

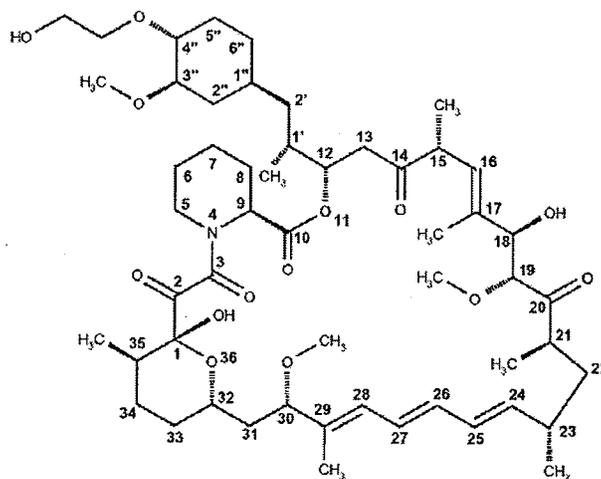


Figure 1. IUPAC Name Numbering System

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 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).

b(4)

Chemistry Review Data Sheet

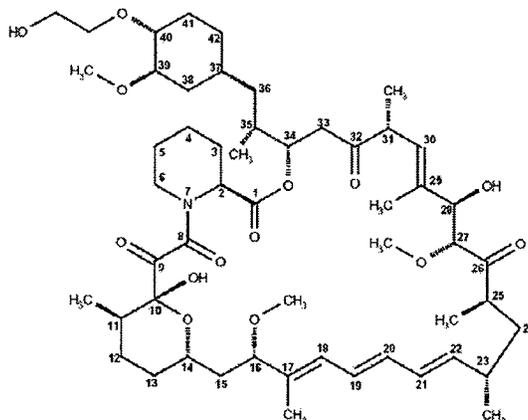


Figure 2. Numbering System Used by Novartis

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

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

b(4)

<sup>1</sup> 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")

<sup>2</sup> 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	_____	Commercial IND

18. STATUS:

b(4)

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



Executive Summary Section

The Chemistry Review for NDA [redacted] etc. b(4)  
(Drug Substance Only)

The Executive Summary

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

Reference Number	Indication	Status
NDA [redacted]	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 [redacted]		AE 03-DEC-2003
NDA [redacted]		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 [redacted] can be approved. b(4)  
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. Everolimus, or 40-O-(2-hydroxyethyl)-rapamycin, is obtained through

b(4)

Everolimus is soluble. Like sirolimus, everolimus is Because of this butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an

b(4)

See NDA specific drug product reviews (NDA 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

✓

b(4)

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). **b(4)**

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        (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 impurity       . A revised validation report was submitted to NDA 22-334 on January 20, 2009. As a result, the proposed structure of        has been revised and a new        established. Previous testing may have slightly overestimated the amount of        actually present. The acceptance criterion for        has been tightened from       . **b(4)**

Additional long-term stability data have been collected at -20°C and 5°C. The results support the proposed retest period of        for drug substance stored at 2-8°C. **b(4)**

Note that, from the clinical perspective, NDA        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**

{see dfs}

53 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Mark Seggel  
3/4/2009 05:06:31 PM  
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Norman Schmuff  
3/5/2009 08:43:02 AM  
CHEMIST

**Initial Quality Assessment  
Branch V  
Pre-Marketing Assessment Division III  
Office of New Drug Quality Assessment**

**OND Division:** Division of Drug Oncology Products  
**NDA:** 22-334 (electronic submission)  
**Applicant:** Novartis Pharmaceutical Corp.  
**Letter Date:** 27 January, 2008  
**Stamp Date:** 30 January, 2008  
**PDUFA Goal Date:** 30 April, 2008 (priority)  
**Trade Name:** Afinitor  
**Established Name:** Everolimus (formerly RAD001)  
**Dosage Form:** Tablet – 5 mg and 10 mg  
**Route of Administration:** Oral  
**Indication:** Treatment of Advanced Renal Cell carcinoma.

**Regulatory Filing** For 505 (b) (1)  
**Related IND** IND 66,279, \_\_\_\_\_ NDA [ ] NDA 21-628 **b(4)**  
and DMF \_\_\_\_\_  
**Assessed by:** Haripada Sarker

Yes No

**ONDQA Fileability:** x

**Comments for 74-Day Letter:** x

**Background Summary**

The application introduces the drug product, Everolimus Tablet. The tablet formulation is intended for use in patients with Treatment of Advance Renal Cell Carcinoma. Everolimus has been formulated as 5 mg and 10 mg tablets for oral administration. Lower strengths of everolimus tablets (0.25 mg, 0.5 mg, 0.75 mg and 1 mg) are marketed in more than 60 countries in the transplant setting under the trade name Certican. Everolimus has been in clinical development as an investigational immunosuppressant drug for transplantation under \_\_\_\_\_ since 1996. Two NDAs for everolimus have been previously submitted by Novartis Pharmaceutical for use in transplant patients for which approval is pending: NDA [ ] for the prophylaxis of organ rejection in allogenic kidney transplantation and NDA 21-628 for the prophylaxis of organ rejection in cardiac transplantation. Since November 2002, everolimus has also been in development to treat cancer patients both as monotherapy and \_\_\_\_\_ under IND 66,279. **b(4)**

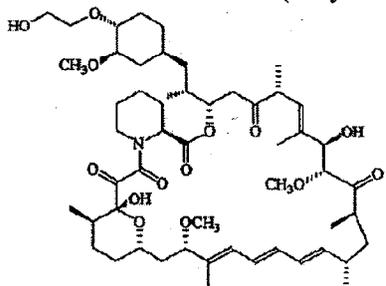
Applicant referred to unapproved NDAs for drug substance CMC information. In pre-NDA meeting held on April 3, 2008 under IND 66,279 several CMC issues were discussed. One of the issues was whether Novartis can cross-refer to drug substance information in the pending Certican NDA and 21-628 submitted to the Division of Special Pathogen and Transplant Products respectively. Agency's response was acceptable, however, it was not clear whether the acceptability refers to approved NDAs or not, and the issue is still undergoing discussion. The CMC information of the NDA is submitted as per CTDQ format.

### Drug Substance (DS)

The drug substance (RAD001: everolimus; 40-O-(2-hydroxyethyl)-rapamycin) is a macrocyclic lactone which is derived by \_\_\_\_\_ from the natural product rapamycin. Applicant referred to pending NDAs \_\_\_\_\_ and 21-628 for all drug substance CMC information. Since the approval of these reference NDAs are pending, communication has been made with the applicant to provide full DS information in the NDA submission. Request has been made to office of compliance to provide inspection reports for the DS related sites listed in the submission. The DS is identified with following structure.

b(4)

Chemical Name: 40-O-(2-hydroxyethyl)-rapamycin



### DS Critical Issues

- Drug substance full CMC information yet to be provided from pending reference NDAs \_\_\_\_\_ and 21-628.
- The cross-referred NDAs \_\_\_\_\_ and 21-628 for DS information should be evaluated to support the submitted NDA. Specifically, any change in DS manufacturing site, specification or stability in reference NDAs.
- EER information for DS and DP needs to be re-examined for any change in sites in reference NDAs and the submitted NDA.

b(4)

### Drug Product (DP)

The DP, RAD001, has been formulated as 5 mg and 10 mg tablets contain everolimus as the active drug substance. The tablet formulation contains the API and the following compendial (USP/NF) excipients: Lactose anhydrous, Anhydrous lactose, Crospovidone, Hypromellose, \_\_\_\_\_ Lactose monohydrate, Magnesium stearate, Butylhydroxytoluene, Butylated hydroxytoluene, \_\_\_\_\_

b(4)

The drug product is manufactured by \_\_\_\_\_

b(4)

b(4)

The main DP manufacturing site

is listed below:

Novartis Pharma AG  
Lichtstrasse 35  
CH-4056 Basel  
Switzerland

┌

b(4)

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Stability study is conducted on 2.5mg, 5mg and 10mg tablets. Analytical data are available for up to 18 months on 3 batches each of 2.5 mg and 10 mg as per the proposed bracketing agreement in the meeting minutes of Pre-NDA meeting of 03-Apr-2008. The stability profiles are tested under long term (25°C/60% RH; 30°C/65% RH), accelerated (40°C/75% RH, 6 months) and supportive stability studies. Supportive stability studies are presented for a total of 7 clinical batches of RAD001 2.5 mg, 5 mg and 10 mg tablets

The Applicant proposes \_\_\_\_\_ expiration dating period for the RAD001 5 mg and 10 mg tablets, Store at 25 °C (77 °F); excursions permitted to 15 – 30 °C (59 – 86 °F); protect from light and moisture.

*Drug Product Critical Issues*

- Comparative impurity profiles of DP with that of DS in reference NDAs.
- Check issues on Executed batch records and Registration stability plans are met as discussed in pre-NDA meeting.
- In-process controls, sampling in blend uniformity method, hardness of the tablet and content uniformity need to be evaluated to find any interrelation.
- Justification of dissolution method and specification including the dissolution media that will discriminate the DP. Any relation between tablet hardness and dissolution.
- Critical relation between \_\_\_\_\_ should be justified.
- \_\_\_\_\_
- Verify the stability data of 5mg tablet under supportive stability studies, because one 5 mg batch (X065 0504) did not comply with the specifications due to failure in packaging operation.

b(4)

- Monitor the integrity of blister packaging with respect to the stability of DP.

**Fileability Template**

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Tentatively.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Apparently YES
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CB ER LNC DMETS/ODS <b>EER</b>

**Have all DMF References been identified? Yes (√) No ( )**

DMF Number	Holder	Description	LOA Included
			Yes

**b(4)**

**Comments and Recommendations**

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. A single reviewer is recommended for this NDA, since the manufacturing process is not particularly complex.

Haripada Sarker  
Pharmaceutical Assessment Lead (PAL)

August 4, 2008  
Date

Sarah Pope, Ph.D.  
Acting Branch Chief

August 4, 2008  
Date

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/s/

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Haripada Sarker  
8/4/2008 11:25:10 AM  
CHEMIST

Sarah Pope  
8/5/2008 02:53:37 PM  
CHEMIST



EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2008				KASLIWALR
OC RECOMMENDATION	24-JUL-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN 9611204 FEI 3002807772

NOVARTIS PHARMA AG  
 LICHSTRASSE 35, ST. JOHANN SITE  
 BASEL, , SZ

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 FINISHED DOSAGE MANUFACTURER

Profile: CSN OAI Status: NONE

Es s. Comment: THE FACILITY MANUFACTURES THE EVEROLIMUS DRUG SUBSTANCE BY \_\_\_\_\_  
 \_\_\_\_\_ RAMPAMYCIN.  
 THE FACILITY ALSO MANUFACTURES \_\_\_\_\_ (AN IN  
 PROCESS MATERIAL) USED IN DRUG PRODUCT MANUFACTURE. (on 22-JUL-2008 by

b(4)

## ESTABLISHMENT EVALUATION REQUEST

## DETAIL REPORT

R. KASLIWAL ( ) 301-796-1386)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2008				KASLIWALR
SUBMITTED TO DO	24-JUL-2008	PS			ADAMSS
ASSIGNED INSPECTION T	29-JUL-2008	PS			ADAMSS
INSPECTION SCHEDULED	21-OCT-2008		21-NOV-2008		IRIVERA
INSPECTION PERFORMED	21-NOV-2008		21-NOV-2008		KATHERINE.J

This foreign preapproval and drug GMP inspection of an active pharmaceutical ingredient (API) manufacturer, and release tester for drug substances and finished dosage forms was conducted per compliance program 7356.002F, Active Pharmaceutical Ingredient (API)

Process Inspection, and compliance program, 7346.832, Pre-Approval

Inspections/Investigations, under FACTS assignment 4719035. The firm has adopted and implemented regulatory guidance ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Mr. Thomas Strubin The following applications and profile classes were covered:

NDA 22268/000 Artemether / Lumefantrine (Profile Class: CTX)

NDA 22334/000 Everolimus (Profile Classes: CSN, NEC, CTX)

The most recent inspection of this site was a Commercial Sponsor Bioresearch Monitoring Inspection conducted on 10/27/08 -11/06/08. No FDA 483 was issued.

The previous inspection of the Novartis Pharma AG, Chemical Operations Basel site was conducted on 6/01-02/2005. That inspection was a pre-approval inspection covering the manufacture and testing of the non-sterile API, ICL670. This API was intended for use in the production of Deferasirox 125, 250 and 500mg Dispersible Tablets, NDA 21-882. That inspection which included a review of the operations at the Novartis Pharma ChemOps CH sites in Schweizerhalle, Basel and Stein resulted in a one-item FDA 483. Specifically,



ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

ASSIGNED INSPECTION T	29-JUL-2008	PS		ADAMSS
INSPECTION SCHEDULED	21-OCT-2008		21-NOV-2008	IRIVERA
INSPECTION PERFORMED	21-NOV-2008		21-NOV-2008	KATHERINE.J

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED  
This foreign preapproval and drug GMP inspection of an active pharmaceutical ingredient (API) manufacturer, and release tester for drug substances and finished dosage forms was conducted per compliance program 7356.002F, Active Pharmaceutical Ingredient (API) Process Inspection, and compliance program, 7346.832, Pre-Approval Inspections/Investigations, under FACTS assignment 4719035. The firm has adopted and implemented regulatory guidance ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. Mr. Thomas Strubin The following applications and profile classes were covered:

NDA 22268/000 Artemether / Lumefantrine (Profile Class: CTX)  
NDA 22334/000 Everolimus (Profile Classes: CSN, NEC, CTX)

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samples were deficient and not performed in accordance with the firm's procedures for evaluating such test results. Corrections to this FDA 483 item were provided during the inspection.

The current FDA inspection conducted

DO RECOMMENDATION	23-FEB-2009	ACCEPTABLE	ADAMSS
		ADEQUATE FIRM RESPONSE	
		INSPECTION	
OC RECOMMENDATION	23-FEB-2009	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	

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Establishment: CFN 9612715 FEI 3002807776  
NOVARTIS PHARMA AG  
CORK  
RINGASKIDDY, CORK, , EI

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2008				KASLIWALR
SUBMITTED TO DO	24-JUL-2008	GMP			ADAMSS
ASSIGNED INSPECTION T	19-AUG-2008	GMP			ADAMSS
INSPECTION PERFORMED	25-NOV-2008				CHARISSE.GR

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

DO RECOMMENDATION	02-DEC-2008			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	02-DEC-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
INSPECTION PERFORMED	22-DEC-2008				CHARISSE.GR

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

Establishment: CFN 9692043 FEI 3002653483  
 NOVARTIS PHARMA STEIN AG  
 SCHAFFHAUSERSTRASSE  
 STEIN, , SZ

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM OAI Status: NONE

Estab. Comment: THE FACILITY PERFORMS \_\_\_\_\_ AND  
 MANUFACTURE OF TABLETS. THE QUALITY CONTROL OF 5MG AND 10 MG TABLETS IS  
 ALSO PERFORMED. (on 22-JUL-2008 by R. KASLIWAL () 301-796-1386)

b(4)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2008				KASLIWALR
ADMITTED TO DO	24-JUL-2008	PS			ADAMSS
DO RECOMMENDATION	29-AUG-2008			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
NAI GMP EI 9/2007					
OC RECOMMENDATION	04-SEP-2008			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 2416082 FEI 2416082  
NOVARTIS PHARMACEUTICALS CORP  
OLD MILL RD  
SUFFERN, NY 10901

DM No: AADA:  
Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CTX OAI Status: NONE

## ESTABLISHMENT EVALUATION REQUEST

## DETAIL REPORT

Estab. Comment: STABILITY TESTING OF TABLETS IS PERFORMED. (on 22-JUL-2008 by R. KASLIWAL () 301-796-1386)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2008				KASLIWALR
OC RECOMMENDATION	24-JUL-2008			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN 9614433 FEI 3002807773  
 NOVARTIS PHARMANALYTICA SA  
 VIA SERFINO BLESTRA 31  
 LOCARNO, , SZ

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: QUALITY CONTROL WITH THE EXCEPTION OF MICROBIOLOGY AND STABILITY TESTING OF \_\_\_\_\_ IS PERFORMED. (on 22-JUL-2008 by R. KASLIWAL () 301-796-1386)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2008				KASLIWALR
OC RECOMMENDATION	24-JUL-2008			ACCEPTABLE BASED ON PROFILE	ADAMSS

b(4)

Establishment: CFN 9610016 FEI 3002806523

SANDOZ GMBH

BIOCHEMIESTRASSE 10

6250 KUNDL, TYROL, , AU

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile:

CFN

OAI Status:

NONE

Estab. Comment: THE FACILITY MANUFACTURES RAMPAMYCIN (FERMENTATION PROCESS). (on 22-JUL-2008 by R. KASLIWAL () 301-796-1386)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	22-JUL-2008				KASLIWALR
SUBMITTED TO DO	24-JUL-2008	GMP			ADAMSS
DO RECOMMENDATION	10-JAN-2009			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	11-JAN-2009			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

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ON ORIGINAL**