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).

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): $C_{33}H_{66}NO_{14}$ and the molecular weight is 958.22.


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.

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 each and the 10 mg tablets weight each.

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

/s/
----------------------
Richard Lostritto
3/26/2009 02:07:37 PM
CHEMIST
NDA 22-334

Afinitor®
(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.

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7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPET:

a) Proprietary Name: Afinitor®
b) Non-Proprietary Name (USAN): everolimus
c) Code Name/# (ONDC only): RAD 001
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):
   - X Not a SPOTS product

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

![Chemical Structure Diagram]

Chemical Formula: C_{23}H_{32}NO_{14}
Molecular Weight: 958.22
Elemental Analysis: C, 66.43; H, 8.73; N, 1.46; O, 23.38

17. RELATED/SUPPORTING DOCUMENTS:
   A. DMFs:
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.

Review was performed by Dr. Mark R. Seggel

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")

Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

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<td>IND</td>
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<td>Commercial IND to study transplant indication.</td>
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<td>21-628</td>
<td>Sponsor’s NDA for same drug substance and similar drug product (different strengths) submitted (not approved) for heart transplant indication.</td>
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**ONDC:**

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<td>26-Jan-2009</td>
<td>Shwu-Luan Lee, Ph.D.</td>
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<td>Proposed trademark, Afinitor is acceptable.</td>
<td>11-Aug-2008</td>
<td>Melina Griffis, R.Ph.,</td>
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<td>EA</td>
<td>Claim for categorical exclusion is acceptable</td>
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<td>Ravindra K. Kasliwal, Ph.D.</td>
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<td>Microbiology</td>
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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 500 mg, 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-hydroxyethyl)-3-methoxycyclohexyl}-1-methylethyl}-19,30- dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-aza-tricyclo[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 by the

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
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.

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.

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.
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
Page(s) Withheld

✓ Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Draft Labeling (b5)

Deliberative Process (b5)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Ravi Kasliwal
3/17/2009 08:06:07 AM
CHEMIST

Sarah Pope
3/18/2009 11:35:17 AM
CHEMIST
NDA 22-334*

*Afinito® (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: 22-334 (and associated NDAs 21-628)

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

3. REVIEW DATE: March 4, 2009

4. REVIEWER: Mark R. Seggel

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7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation
8. DRUG PRODUCT NAME/CODE/TYPEx:
   a) Proprietary Name: 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 21-628: 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: 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:
Everolimus:


![IUPAC Name Numbering System](image)

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).
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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Action codes for DMF Table:
1 – DMF Reviewed.
2 – Type I 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”)

Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

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<td>S. Adams, HFD-325</td>
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The Chemistry Review for NDA etc. (Drug Substance Only)

The Executive Summary

Everolimus is the active ingredient in several Novartis applications. All use the same everolimus BHT.

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<td>NDA 21-628</td>
<td>Certican® Tablets; Prophylaxis of organ rejection in allogeneic renal transplant recipients</td>
<td>AE 20-OCT-2003</td>
<td>AE 27-AUG-2004 (for Clinical)</td>
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<td>Afinitor® Tablets; Treatment of advanced renal cell carcinoma</td>
<td>Under review in DDOP/OODP</td>
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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 21-628 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.
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 

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

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

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...
CHEMISTRY REVIEW #3

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 (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 .

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.

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.
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)

Withheld Track Number: Chemistry-2
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Mark Seggel
3/4/2009 05:06:31 PM
CHEMIST

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
Assessed by: Haripada Sarker

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 Advanced 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.
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 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.

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

\[
\text{HO-} \quad \text{O} \quad \text{CH}_2 \text{O} \quad \text{CH}_2 \text{O} \quad \text{OH} \quad \text{CH}_3 \quad \text{OH} \quad \text{CH}_3
\]

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.

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,

The drug product is manufactured by

---

b(4)
The main DP manufacturing site is listed below:

Novartis Pharma AG  
Lichtstrasse 35  
CH-4056 Basel  
Switzerland

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

### Fileability Template

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<td>3. Is the section legible?</td>
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<td>6. Has an environmental assessment report or categorical exclusion been provided?</td>
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<tr>
<td>8. Does the section contain controls for the drug product?</td>
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<td>9. Has stability data and analysis been provided to support the requested expiration date?</td>
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<td>15. Is a separate microbiological section included?</td>
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<td>16. Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)</td>
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**Microbiology**
- Pharm/Tox
- Biopharm
- Statistics
- (stability)
- OCP/CDRH/CB
- ER
- LNC
- DMETS/ODS
- EER

Have all DMF References been identified? Yes (✓) No ( )

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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)

Sarah Pope, Ph.D.
Acting Branch Chief

August 4, 2008
Date

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

/s/

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

Sarah Pope
8/5/2008 02:53:37 PM
CHEMIST
ESTABLISHMENT EVALUATION REQUEST
DETIAL REPORT

Application: NDA 22334/000
Action Goal:

Stamp: 30-JUN-2008
District Goal: 01-MAR-2009

Regulatory Due: 31-MAR-2009
Brand Name: AFFINITOR

 Applicant: NOVARTIS PHARMS
Estab. Name: Affinitor
1 HEALTH PLAZA
EAST HANOVER, NJ 07936-1080

Generic Name: EVEROLIMUS

Priority: 1P
Dosage Form: (TABLET)

Org Code: 150
Strength: 5 MG AND 10 MG

Application Comment: THIS IS AN ONCOLOGY PRIORITY NDA. THE FACILITIES IN THIS NDA HAVE BEEN PREVIOUSLY ALSO SUBMITTED AS PART OF THE NDA — (on 09- OCT-2008 by R. KASLIWAL () 301-796-1386)

FDA Contacts: D. WOODY (HFV-230) 240-276-9237 , Project Manager
R. KASLIWAL 301-796-1386 , Review Chemist
ID = 124115 , Team Leader

Overall Recommendation: ACCEPTABLE on 23-FEB-2009 by S. ADAMS (HFD-325) 301-796-3193

Establishment: CFN FEI

DMF No: AADA:

Responsibilities: b(4)

Profile: TCM OAI Status: NONE
Establishment:  CFN  9611204  FEI  3002807772

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

DMF No:  
Responsibilities:  DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
Profile:  CSN  OAI Status:  NONE

Em. J. 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
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) 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,
the procedure for investigating/evaluating Out-of-Specification and Out-of-Expectation test results was found deficient. Investigations performed when OOS and OOE test results obtained for the intermediate, final drug substance (prior to b(4) and stability ples 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 on 11/17/08 ? 11/21/08 included a review of the

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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

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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

**OC RECOMMENDATION** 23-FEB-2009

---

**Establishment:** CFN 9612715  FEI 3002807776

NOVARTIS PHARMA AG
CORK
RINGASKIDDY, CORK, , EI

**DMF No:**

**Responsibilities:** DRUG SUBSTANCE STABILITY TESTER
Profile: CTL
OAI Status: NONE

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

DO RECOMMENDATION 02-DEC-2008 ACCEPTABLE ADAMSS
OC RECOMMENDATION 02-DEC-2008 ACCEPTABLE 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

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

DV No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTX
OAI Status: NONE
Estab. Comment: STABILITY TESTING OF TABLETS IS PERFORMED. (on 22-JUL-2008 by R. KASLIWAL (301-796-1386))

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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))

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BASED ON PROFILE
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


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