

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203985Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA #	NDA 203985	
Product Name:	Afinitor Disperz® Tablet for Oral Suspension	
PMR/PMC Description:	Dissolution Method Development Report and Prior Approval Supplement (including the revised dissolution method and information to support the dissolution acceptance criterion)	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>N/A</u>
	Study/Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>03/29/2013</u>
	Other: Prior Approval Supplement Submission:	<u>08/29/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant will conduct additional studies to develop a discriminating dissolution method. In an email to Ms. Jewell Martin (ONDQA Product Quality Regulatory Project Manager) dated July 25, 2012, the Applicant agreed to submit a dissolution development report to the Agency by 02/29/2013. The Agency agreed to review the report and provide feedback within 30 days. If the Agency deems the revised dissolution method acceptable, the Applicant will submit a prior approval supplement including 1) the revised dissolution method, and 2) dissolution data for stability and release batches available at the time of submission. This prior approval supplement will be submitted to the Agency by 08/29/2013.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

VAISHALI JARRAL
08/03/2012

JEFFERY L SUMMERS
08/06/2012

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In response to the FDA request for USP <671> results for Water Vapor Transmission Rate for the blister packaging system, the applicant stated in the 13-Jul-2012 amendment that the blister packaging system proposed for marketing is slightly different from that used in registration stability studies. (b) (4)
Per ICH Q1A(R2), testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. The Agency requested that the applicant submit USP <671> results for the proposed packaging system, as well as stability data for the drug product packaged in the proposed commercial container closure system showing comparable results with the registration stability data.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The applicant agrees to conduct pre-validation as well as validation activities for the blistering process for the container closure system that will be used for the US market. The USP <671> Water Vapor Transmission Rate test (WVTR) will be performed with blister cards derived from Pre-Validation trials. The most stringent requirement, Class A <0.5 mg/day, will need to be met before proceeding with validation and launch activities.

To bridge the registration stability and the launch batches Novartis will ensure that the WVTR result is comparable to that measured for the registration stability batches.

Novartis will provide the comparable USP<671> WVTR data before the end of November 2012. Novartis also commits to submitting the 3 months accelerated stability data on the first 3 commercial batches before the end of May 2013.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

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- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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Other

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 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

VAISHALI JARRAL
08/03/2012

JEFFERY L SUMMERS
08/06/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 25, 2012

To: Vaishali Jarral, Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Karen Munoz-Nero, BSN, RN, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

CC: Carole Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion, OPDP

Subject: **AFINITOR® DISPERZ (everolimus) tablets for oral suspension
NDA 203985
OPDP Comments on proposed patient package insert**

In response to the Division of Oncology Products 2 (DOP 2) March 06, 2012, consult request, DCDP has reviewed the proposed patient package insert (PPI) for AFINITOR® DISPERZ (everolimus) tablets for oral suspension.

DCDP's comments for the PPI are based on the completed Division of Medical Policy Programs (DMPP) revised labeling entitled "Everolimus (AFINITOR DISPERZ) N203985 DMPP PPI Jul-2012 clean.doc" sent via electronic mail from Sharon Mills, BSN, RN, CCRP, Senior Patient Labeling Reviewer of DMPP on July 24, 2012. It is noted that the DMPP review was based on the PPI version of July 11, 2012.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions regarding this consult review, please contact Karen Munoz-Nero at 301-796-3274 or Karen.Munoz@fda.hhs.gov.

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/s/

KAREN MUNOZ-NERO
07/25/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: July 24, 2012

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP 2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI), Instructions for Use (IFU)

Drug Name (established name): AFINITOR DISPERZ (everolimus)

Dosage Form and Route: tablets for oral suspension

Application Type/Number: NDA 203-985

Applicant: Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On February 29, 2012, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original New Drug Application (NDA) 203-985 for AFINITOR DISPERZ (everolimus) tablets for oral suspension. The Applicant's submission is in response to a formal Written Request (WR) letter made to NDA 22-334 Afinitor tablets dated April 1, 2010, and provides outstanding components outlined in the WR letter in support of a proposed pediatric-appropriate formulation of Afinitor (everolimus). On March 6, 2012, the Division of Oncology Products 2 (DOP 2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use for AFINITOR DISPERZ (everolimus) tablets for oral suspension.

This review is written in response to a request by DOP 2 for DMPP to review the Applicant's proposed Patient Package Insert (PPI), Instructions for Use (IFU) for AFINITOR DISPERZ (everolimus) tablets for oral suspension

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on July 13, 2012.

2 MATERIAL REVIEWED

- Draft AFINITOR DISPERZ (everolimus) tablets for oral suspension Patient Package Insert (PPI) and Instructions for Use (IFU) received on February 29, 2012, further revised and received on April 3, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on July 11 2012.
- Draft AFINITOR DISPERZ (everolimus) tablets for oral suspension Prescribing Information (PI) received on February 29, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on July 11, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFU document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 DISCUSSION

On March 21, 2012, DOP 2 sent an Information Request Letter to the Applicant which provided DMPP comments and request for information regarding their PPI. The letter requested that the Applicant develop separate Instructions for Use (IFU) rather than to include them within the body of the PPI and to simplify the language. The Applicant responded to this Information Request on April 3, 2012 with a revised PPI and IFU.

5 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

6 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI and IFU are appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
07/24/2012

LASHAWN M GRIFFITHS
07/24/2012

Internal Consult

****Pre-decisional Agency Information****

To: Vaishali Jarral, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion
Office of Prescription Drug Promotion (OPDP)

Cc: Karen Munoz, Regulatory Review Officer
Division of Direct-to-Consumer Promotion, OPDP

Date: July 20, 2012

Re: **AFINITOR DISPERZ (everolimus tablets for oral suspension)**
NDA 203985
OPDP Labeling Comments

In response to the Division of Oncology Products 2 (DOP 2) March 6, 2012, consult request, OPDP has reviewed proposed labeling (Package Insert (PI) and carton/container) for AFINITOR. OPDP comments for the proposed patient package insert (PPI) will be provided in a separate consult response.

OPDP's comments for the PI are based on the substantially complete draft labeling sent via electronic mail to OPDP from DOP 2 on July 11, 2012. OPDP's comments are provided directly in the attached document. Please note that for the PI, OPDP hid deletions and formatting changes so that OPDP comments are easier to read.

The proposed carton and container labeling used in this review may be found in the original application (folder 0013) dated June 22, 2012, at EDR location: \\CDSESUB1\EVSPROD\NDA203985\203985.enx. OPDP does not have comments on the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CAROLE C BROADNAX
07/20/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: July 12, 2012

Reviewer: James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, Pharm.D., MPH
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Afinitor Disperz (Everolimus) Tablets for Oral Suspension;
2 mg, 3 mg, and 5 mg

Application Type/Number: NDA 203985

Applicant: Novartis

OSE RCM #: 2012-561

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Afinitor Disperz (Everolimus) Tablets for Oral Suspension (NDA 203985) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Afinitor (Everolimus) immediate release tablets submitted under NDA 022334 were originally approved on March 30, 2009 for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. On October 20, 2010, Afinitor received approval for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis in patients three years old or older that required therapeutic intervention but were not candidates for curative surgical resection. On May 5, 2011, Afinitor was approved for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable locally advanced or metastatic disease. Everolimus was also approved under the brand name, Zortress, on April 20, 2010 as a dual trade name for prophylaxis of organ rejection in adult patients at low to moderate immunologic risk receiving a kidney transplant.

The sponsor is currently seeking approval for the treatment of SEGA to patients less than three years old. Because of this new pediatric population subset, a dispersible suspension formulation is proposed to provide an appropriate dosage form for this patient population, Afinitor Disperz. This is the subject of this review.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 2, 2012 proprietary name submission.

- Active Ingredient: Everolimus
- Indication of Use: Treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis in patients that require therapeutic intervention but are not candidates for curative surgical resection.
- Route of Administration: Orally
- Dosage Form: Tablets for Oral Suspension
- Strength: 2 mg, 3 mg, 5 mg
- Dose and Frequency: 4.5 mg/m² once daily rounded to the nearest dose that can be achieved with a whole tablet or tablets. The dose of Afinitor is reduced by 50% if moderate CYP3A4 inhibitors are taken concurrently. If strong CYP3A4 inducers are used concurrently, the Afinitor dose should be doubled. Dose adjustments should be made based on achieving steady state trough levels between $\frac{(b)}{(4)}$ ng/mL to 15 ng/mL.

- How Supplied: White to slightly yellowish, round, flat tablets with a beveled edge and no score. The 2 mg tablet is engraved with “D2” on one side, the 3 mg tablet with “D3”, and the 5 mg tablet with “D5”. All tablet strengths have “NVR” engraved on the other side.
- Storage: Store Afinitor Disperz at room temperature. Excursions are allowed between 59°F to 86°F (15°C to 30°C).
 - Keep Afinitor Disperz in the package it comes in.
 - (b) (4)
 - Keep the blister package and tablets dry prior to taking.
 - Keep Afinitor Disperz out of light.
- Container and Closure Systems: Each carton contains 4 blister cards of 7 tablets each for a total of 28 tablets per carton.

Afinitor tablets (NDA 022334) are marketed in the following strengths: 2.5 mg, 5 mg, 7.5 mg, and 10 mg.

2 METHODS AND MATERIALS REVIEWED

Because Afinitor immediate release tablets are currently marketed, DMEPA searched the FDA AERS database for Afinitor medication error reports and conducted a literature search. We also reviewed the Afinitor Disperz container labels, carton labeling, and package insert labeling submitted by the Applicant as well as the Afinitor container labels and carton labeling. Lastly, DMEPA obtained samples of Afinitor Disperz tablets for oral suspension to assess the dispersion of the tablets in an oral syringe or glass using the instructions in the insert labeling.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) using the strategy listed in Table 1. The last AERS search conducted for Afinitor was June 17, 2011 in OSE review 2011-2264.

Table 1: AERS Search Strategy	
Date	April 27, 2012 Date Range: June 17, 2011 – April 27, 2012
Drug Names	Everolimus Afinitor Afin% and Ever%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search identified 20 reports. Each report was reviewed for relevancy and duplication. After individual review, 8 reports were not included in the final analysis for the following reasons:

- Medication error not related to Afinitor
- Adverse events not related to medication errors

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on June 1, 2012 for additional cases and actions concerning Afinitor. There were no additional medication error cases reported. Additionally, we did not find any cases or articles that discussed the preparation of the suspension for pediatric patients.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 8, 2012 (Appendix B)
- Carton Labeling submitted June 8, 2012 (Appendix C)
- Insert Labeling submitted May 29, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the Afinitor Disperz product design as well as the associated label and labeling.

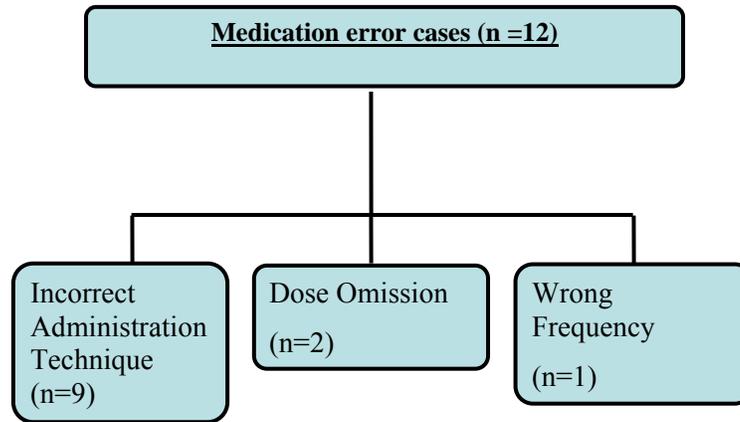
3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, 12 Afinitor Disperz medication error cases remained for our detailed analysis. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of cases included in the review by type of error. Appendix F provides listings of all ISR numbers for the cases summarized in this review.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Figure 1: Afinitor Disperz medication errors (n =12) categorized by type of error



- Incorrect Administration Technique

Incorrect administration technique was the most frequently reported error.

- Seven cases involved the splitting of tablets and administration of the drug. The outcomes in each case were not reported.
- Two cases involved the crushing or chewing of the tablet with applesauce. The outcomes were reported as unchanged or unknown.

No additional information explaining the cause of the error was provided. Therefore, we are unable to determine if the patient was instructed to administer the product in this fashion or if they chose this method on their own accord. DMEPA found the currently marketed Afinitor labeling to have adequate statements to take the tablets whole, to not crush the tablet, and to not take broken tablets.

- Dose Omission - Two cases involved the patient missing a dose. No further information explaining the cause of the error or information on the outcome was provided.
- Wrong Frequency - One case involved the patient taking Afinitor once daily for four weeks, then taking two weeks off, before taking Afinitor again daily for four weeks. No further information explaining the cause of the error or information on the outcome was provided. The case did not provide information on whether the drug was prescribed with a 2 week rest period or if the patient chose this regimen on their own accord.

3.2 ASSESSMENT OF THE DISPERSION OF AFINITOR DISPERZ IN WATER

The instructions give the patient or caregiver the option to prepare the dose in an oral syringe or small glass. Therefore, DMEPA requested samples of Afinitor Disperz. The samples were obtained from the Applicant to assess how quickly and completely the tablets disperse in water using the proposed instructions for use located in the insert labeling. After following the instructions, the tablets completely dispersed within the 3 minute time frame noted in the instructions for both methods of preparation.

3.3 ASSESSMENT OF LABELS AND LABELING

DMEPA identified deficiencies in the labels and labeling and have provided recommendations in Section 4 to correct these deficiencies and help minimize the risk of medication errors.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Container Label
 - 1. Add the statement above the scissor graphic “Store in original container; protect from light and moisture.”
- B. Physician Sample Container Labels
 - 1. Per 21 CFR 203.38(c), revise to clearly denote the status as a drug sample. For example, use the word “Sample” on the label.
- C. Carton Labeling
 - 1. Revise the presentation of the proprietary name from all upper case letters (AFINITOR DISPERZ) to title case (Afinitor Disperz) to improve readability.
 - 2. Ensure that the colors used to differentiate the product strengths on the carton labeling are also the same colors utilized for the corresponding container labels.
- D. Insert Labeling
 - 1. General Comments
 - a. Due to the drug’s potential for reproductive toxicity, DMEPA recommends the division consider the addition of safe handling of hazardous drug information language to the package insert and instructions for use to promote the safe use among patients and caregivers. DMEPA and DOP2 added the following statements to the introduction of Instructions for Use (IFU).

“AFINITOR DISPERZ may cause harm to an unborn child. When possible, the suspension should be prepared by an adult who is not pregnant or planning to become pregnant. Anyone who prepares suspensions of AFINITOR DISPERZ for another person should wear gloves and face mask to avoid possible contact with the drug.”
 - 2. Highlights of Prescribing Information
 - a. Dosage and Administration
SEGA with TSC:

Add the statement - 4.5 mg/m² once daily rounded to a dose obtained by using whole tablet(s): adjust dose to attain trough concentrations of (b) (4) ng/mL.

3. 2.1 Dosage

Recommended Dose

- a. Revise the second bullet point statement under *Recommended Dose*:

‘SEGA with TSC: Individualize dose based on body surface area (calculated using the Dubois formula). The recommended starting dose is 4.5 mg/m², once daily, rounded to the nearest strength of either AFINITOR Tablets or AFINITOR DISPERZ Tablets for Oral Suspension, with subsequent therapeutic drug monitoring to attain trough concentrations of (b) (4) to 15 ng/mL’

to

‘SEGA with TSC: Individualize dose based on body surface area (calculated using the Dubois formula). The recommended starting dose is 4.5 mg/m², once daily, rounded to a dose obtained by using whole tablet(s) of either AFINITOR Tablets or AFINITOR DISPERZ Tablets for Oral Suspension, with subsequent therapeutic drug monitoring to attain trough concentrations of (b) (4)

4. 2.1 Dosage

Dose Modifications

Switching Formulations

- a. Revise the following statement under *Switching Formulations*:

(b) (4)

to

‘Adjust the dose to the closest milligram using whole tablets of the new formulation and assess everolimus trough concentrations approximately 2 weeks later.

5. 15. References

- a. Add references for safe handling of hazardous drugs to Section 15. Section 16, How Supplied/Storage and Handling contains a cross reference to safe handling of hazardous drugs. However, there are no safe handling references listed in Section 15.

E. Instructions for Use

1. General Comments

- a. Revise the first and second sentences in the second paragraph to read:

“Take AFINITOR DISPERZ Tablets for Oral Suspension as a suspension only (a suspension is made of un-dissolved particles of medicine that are mixed with a liquid and taken by mouth). “Do not chew, crush, or swallow the AFINITOR DISPERZ Tablets for Oral Suspension whole.

- b. Each time a figure is referred to, the figure should be directly below or to the side and not in another location such as another page. Ensure each referenced figure is directly below the statement in which it is referenced. As an example, see how step 17 under the oral syringe directions refers the reader back to figure A, two pages back.
- c. Include the Instructions for Use with each carton to ensure the instructions are readily available to the caregiver or patient.

2. Instructions for Use - Oral Syringe

- a. Revise Step 3 to read as follows:

“Note: Doses of 2 mg to 10 mg can be prepared in the oral syringe. If a dose higher than 10 mg is needed, split the dose and prepare a second syringe by repeating steps 2 through 17. Do not break or crush tablets.”

- b. In Step 5, revise the statement (b) (4) ..” to read as follows: “Fill a drinking glass with water only...” since water was the only liquid tested for suspension preparation.
- c. In Step 10, add the statement “Suspension must be used within 60 minutes of preparation.” as the third sentence. The Applicant has not provided data beyond 60 minutes for preparation stability.
- d. In Step 12 and Step 14, write out the instructions for Step 12 and for Step 14 to prevent the patient from having to refer back and forth in the instructions; thus, minimizing the chance for missing a step or performing a step out of order.
- e. In Step 16, instruct the patient or caregiver to thoroughly wash the 2 glasses used in the steps. Provide appropriate graphics as well.

3. Instructions for Use – (b) (4)

- a. In Step 2, revise (b) (4)

to

“Doses of 2 mg to 10 mg can be prepared in the small drinking glass. If a dose higher than 10 mg is needed, split the dose and repeat steps 2 through 7. Do not break or crush tablets.”

If you have further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonization. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES H SCHLICK
07/12/2012

TODD D BRIDGES
07/12/2012

KELLIE A TAYLOR
07/12/2012

CAROL A HOLQUIST
07/13/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

NDA: 203985/0
Product: Afinitor Disperz (everolimus tablet for oral suspension)
Memo Date: 7.12.12
From: Vaishali Jarral, Regulatory Project Manager
Subject: Pediatric Exclusivity Granted for Studies Conducted on Everolimus (RAD001)- Effective Date- July 10, 2012

History:

The Division of Oncology Products 1 issued a Written Request to Novartis on April 1, 2010 re: two studies: Study C2485 (Study 1) and Study M2301 (Study 2) and also asked more information regarding age-appropriate formulation for everolimus. In response to the WR, DOP2 received a new NDA from Novartis on February 29, 2012 (NDA 203985). This NDA included data from Study M2301 and a longer term follow-up date from Study C2485.

NDA 203985 also contained CMC information to support the new tablet formulation of Afinitor [Afinitor Disperz (everolimus tablets for oral suspension)]. Under this NDA, Novartis also requested a pediatric exclusivity determination.

The pediatric exclusivity board meeting was held on July 10, 2012. Conclusion of the meeting was to grant Pediatric exclusivity to Novartis for studies conducted on everolimus (RAD001).

Pediatric Exclusivity Granted- Effective Date- July 10, 2012. The following email was sent to Novartis as a notification on July 12, 2012:

From: Jarral, Vaishali
Sent: Thursday, July 12, 2012 2:34 PM
To: 'Gutman, Nina'
Subject: Pediatric Exclusivity Determination-NDA 203985

Hello Ms. Gutman,

Pediatric Exclusivity has been granted for studies conducted on everolimus (RAD001), effective July 10, 2012, under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). This information will be reflected on CDER's pediatric web site and in the monthly update of the Orange Book.

In accordance with section 505A(e)(1) of the Act, approved drugs for which a pediatric exclusivity determination was made shall have a copy of the Written Request and any amendments posted on CDER's pediatric web site.

In addition, under section 505A(l)(1) of the Act, as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), we remind you of the requirement that for 18 months after pediatric labeling is approved, any report received by FDA of an adverse event associated with the drug granted exclusivity will be referred to the Office of Pediatric Therapeutics. This process occurs for all products granted Pediatric Exclusivity regardless of the regulatory action taken. The Director of that Office will provide for a review of the adverse

event reports by the Pediatric Advisory Committee (PAC) and will obtain recommendations from that Committee on action FDA should take.

Please confirm the receipt of this email.

Thank you,
Vaishali Jarral

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/s/

VAISHALI JARRAL
07/12/2012

AFINITOR is currently classified as a Pregnancy Category D drug, and it is highly likely that women of childbearing age will be preparing this suspension for their children. Please provide recommendations regarding whether the AFINITOR label should include language advising women of childbearing age to use protective measures to avoid exposure while preparing the suspension. There is no data available to assess whether skin contamination with the suspension results in systemic absorption of drug.

INTRODUCTION

On February 29, 2012, Novartis Pharmaceuticals submitted a New Drug Application (NDA) for a pediatric-appropriate formulation of AFINITOR® (everolimus) dispersible tablets for the treatment of patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) and require therapeutic intervention but are not likely to be cured by surgery. This NDA is submitted in response to the April 1, 2010, Pediatric Written Request issued for pediatric studies with everolimus. The suspension dose of the pediatric-appropriate formulation (dispersible tablets) will need to be prepared daily by a caregiver in the home.

The Division of Oncology Products 2 (DDOP2) consulted the Pediatric and Maternal Health Staff - Maternal Health Team (PMHS-MHT) to provide comment on whether AFINITOR labeling should include recommendations for women of childbearing age to use protective measures to avoid exposure while preparing the suspension dose for a child due to findings of embryolethality seen in animals at doses lower than the human clinical dose.

BACKGROUND

Everolimus is an inhibitor of mTOR (mammalian target of rapamycin), a serine-threonine kinase, downstream of the PI3K/AKT pathway. AFINITOR is currently approved for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib; for the treatment of patients with SEGA associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection; and for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease was approved on May 5, 2011. AFINITOR is currently available as uncoated tablets which must be swallowed whole without chewing or crushing.

AFINITOR was classified as a pregnancy category D drug the benefit of using the drug during pregnancy for its approved indications may outweigh, or some patients, the potential risks due to the mechanism of action and demonstrated embryofetal toxicity (pre- and post-implantation losses) observed in animals at doses lower than the human clinical dose. In addition, male infertility was observed in animals at doses lower than the therapeutic dose.

This year, the Centers for Disease Control (CDC) – National Institute for Occupational Safety and Health (NIOSH) is adding everolimus to the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings. Drugs that are considered hazardous include those that exhibit one or more of the following characteristics:¹

- Carcinogenicity

¹ DHHS (NIOSH) Publication Number 2010-167

- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity

Healthcare workers will be required to follow standard precautions along with recommendations included in the manufacturers' material safety data sheet (MSDS)² when handling, preparing, or disposing of everolimus.

DISCUSSION AND CONCLUSIONS

DDOP 2 reports that there are no data available to assess whether skin contamination with Afinitor suspension results in systemic absorption of drug. The MSDS for everolimus states to avoid inhalation and contact with skin, eyes and clothing and that personal protective equipment should be used when handling the product, including respiratory, skin, and eye protection. Based on the information provided by the manufacturer, any caregiver (not limited to women of reproductive age) who prepares Afinitor suspension with the dispersible table should use personal protective equipment during the preparation, administration, and disposal of the product because of the hazard rating of the drug.

RECOMMENDATIONS

- There is a concern for the safe handling of the new formulation AFINITOR DISPERZ Tablets for Oral Suspension and any language advising the use protective measures to avoid exposure while preparing the suspension applies to all caregivers, not just females of reproductive potential or women who are pregnant. Request that the Sponsor submit revised instructions for use for caregivers when handling, preparing, administering, and disposing of Afinitor suspension.

² See Appendix A for the current everolimus MSDS

(b) (4) A

Material Safety Data Sheet - LC Laboratories Cat. No. E-4040 - page 1
Revision Date: May 23, 2011

1. IDENTIFICATION OF SUBSTANCE:

Trade name: Everolimus
Product Number: [E-4040](#)
Manufacturer/Supplier:
LC Laboratories
165 New Boston Street
Woburn, MA 01801 USA
+1-781-937-0777 Fax: +1-781-938-5420

2. COMPOSITION/DATA ON COMPONENTS:

Chemical Name:
Hydroxyethylrapamycin
Synonyms: Afinitor, Certican, SDZ-RAD, RAD001, Zortress
Hazardous Ingredient: 40-*O*-(2-hydroxyethylrapamycin)
CAS Registry Number: 159351-69-6
Molecular Weight: 958.22
Molecular Formula: C₅₃H₈₃NO₁₄

3. HAZARDS IDENTIFICATION:

Hazard Description: potent immunosuppressant; may cause irritation to eyes, skin, mucous membranes

4. FIRST AID MEASURES:

After Inhalation: If inhaled, remove to fresh air; if breathing is difficult, give oxygen; if breathing stops, give artificial respiration
After skin contact: flush with copious amounts of water; remove contaminated clothing and shoes; call a physician
After eye contact: check for and remove contact lenses and flush with copious amounts of water; assure adequate flushing by separating the eyelids with fingers; call a physician
After swallowing: if swallowed, wash out mouth with copious amounts of water; call a physician

5. FIRE FIGHTING MEASURES:

Suitable extinguishing agents: water spray, carbon dioxide, dry chemical powder or foam
Protective equipment: wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.
Unusual fire hazard: none known

6. ACCIDENTAL RELEASE MEASURES:

Person-related safety precautions: cordon off area of spill; wear self-contained breathing apparatus, protective clothing and heavy rubber gloves
Measures for cleaning/collecting: absorb solutions with finely- powdered liquid-binding material (diatomite, universal binders); decontaminate surfaces and equipment by scrubbing with alcohol; dispose of contaminated material according to Section 13

7. HANDLING AND STORAGE:

Information for safe handling: avoid inhalation and contact with skin, eyes and clothing; material may be an irritant

Storage: store solid and solutions at -20 °C

8. EXPOSURE CONTROLS AND PERSONAL PROTECTION:

Personal protective equipment as follows:

Breathing equipment: NIOSH/MSHA-approved respirator

Protection of hands: chemical-resistant rubber gloves

Eye protection: chemical safety goggles

Revision Date: March 21, 2009

9. PHYSICAL AND CHEMICAL PROPERTIES:

Form: solid powder

Color: white to off-white

Odor: none

Melting point/Melting range:

Danger of explosion: none

Solubility in / Miscibility with water: very poorly soluble in water; maximum solubility in plain water is estimated to be about 1-10 μ M; buffers, serum, or other additives may increase or decrease the aqueous solubility

Solvent content: none

Organic solvents: soluble in DMSO at 100 mg/mL; soluble in ethanol at 100 mg/mL

10. STABILITY AND REACTIVITY:

Stability: stable if stored as directed; avoid strong oxidizing agents

Thermal decomposition / conditions to be avoided: protect from light and heat

Dangerous products of decomposition: thermal decomposition may produce toxic gases such as carbon monoxide, carbon dioxide, and nitrogen oxides

11. TOXICOLOGICAL INFORMATION:

RTECS #:

Acute toxicity: none known

Primary irritant effect:

On the skin: none known

On the eye: not known; may be an irritant

12. ECOLOGICAL INFORMATION:

General notes: no data available

13. DISPOSAL CONSIDERATION:

Dispose of in accordance with prevailing country, federal, state and local regulations

14. TRANSPORT INFORMATION:

DOT:

Proper shipping name: none

Non-Hazardous for transport: this substance is considered to be non-hazardous for transport

IATA class:

Proper shipping name: none

Non-Hazardous for transport: this substance is considered to be non-hazardous for transport

15. REGULATIONS:

Code letter and hazard designation of product:

Hazard-determining components of labeling:

Risk phrases: may be irritating to eyes, skin and respiratory system

Safety phrases: in case of accident, flush eyes or skin with copious amounts of water; remove contaminated clothing and shoes; call a physician

16. OTHER INFORMATION:

The above information is believed to be correct based on our present knowledge but does not purport to be complete. For research use only by trained personnel. The burden of safe use of this

material rests entirely with the user. LC Laboratories disclaims all liability for any damage resulting from use of this material.

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/s/

JEANINE A BEST
07/02/2012

MELISSA S TASSINARI
07/02/2012

LISA L MATHIS
07/02/2012

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203985 BLA# N/A	NDA Supplement #:S- 0 BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Afinitor Disperz (everolimus) tablets for oral suspension* Established/Proper Name: everolimus Dosage Form: Tablets for oral suspension Strengths: 2mg, 3mg and 5mg		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A		
Date of Application: 2/29/12 Date of Receipt: 2/29/12 Date clock started after UN: N/A		
PDUFA Goal Date: 8/29/12	Action Goal Date (if different):	
Filing Date: 4/29/12	Date of Filing Meeting: April 5, 2012	
Chemical Classification: 3 (New Dosage Form)		
Proposed indication(s)/Proposed change(s): For the treatment of patients with tuberous sclerosis (complex TSC) who have subependymal giant cell astrocytoma (SEGA) and require therapeutic intervention but are not likely to be cured by surgery.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

* (the name has been revised by the Agency, the original name submitted by Novartis was: Afinitor Disperz (everolimus) (b) (4)

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: COMMENT: Everolimus has received orphan designation for TSC-associated SEGA.	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): INDs 066279				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	YES			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	YES			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	YES			Priority Review
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> <i>If yes, explain in comment column.</i>		NO		
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment

Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		YES			
User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required Additional note: Even though the new indication has an orphan designation, the package insert for the proposed NDA includes an indication that is not designated for a rare disease or condition. As such, Novartis does not meet the exemption from a fee for the proposed NDA and the application required a full NDA fee.			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				NA	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				NA	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				NA	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm				NA	
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity		

			Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	YES			Afinitor tablets

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				<p>Although, Afinitor tablet (different dosage form from the same sponsor) is considered to be 'same', there is no competitor drug that can be considered to be 'same product' according to the orphan drug definition of sameness.</p>
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		NO		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		NO		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
<p>Overall Format/Content</p>	YES	NO	NA	Comment

If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	YES			
Index: Does the submission contain an accurate comprehensive index?	YES			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	YES			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> <i>Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	YES			
Are all establishments and their registration numbers listed on the form/attached to the form?	YES			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	YES			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>	YES			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674." If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	YES			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	YES			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR) If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			NA	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment

<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			NA	
--	--	--	----	--

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		NO		Although this NDA was submitted for the approval of a new dosage form, the indication for which this new dosage form is being proposed, has already been approved and has an Orphan Designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>				
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	YES			
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	YES			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		NO		Risk Management Plan was submitted but not the REMS
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	YES			
Is the PI submitted in PLR format? ⁴	YES			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			NA	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	YES			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	YES			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	YES			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			NA	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			NA	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>			NA	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			NA	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		NO		
	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): October 2, 2007 <i>If yes, distribute minutes before filing meeting</i>	YES			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 27, 2011 <i>If yes, distribute minutes before filing meeting</i>	YES			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		NO		(b) (4)

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 5, 2012

BLA/NDA/Supp #: 203985/0

PROPRIETARY NAME: Afinitor Disperz (everolimus) tablets for oral suspension (the name has been revised by the Agency, the original name submitted by Novartis was: Afinitor Disperz (everolimus) (b)(4))

ESTABLISHED/PROPER NAME: Everolimus

DOSAGE FORM/STRENGTH: 2mg, 3 mg and 5 mg

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) and require therapeutic intervention but are not likely to be cured by surgery.

BACKGROUND: On February 29, 2012, DOP2 received an NDA 203985 from Novartis Pharmaceuticals Corporation for Afinitor Disperz , tablets for oral suspension for treatment of patients with TSC who have SEGA and require therapeutic intervention but are not likely to be cured by surgery. This NDA was submitted to fulfill a Pediatric Written Request and as such also contains a request for pediatric exclusivity determination. Novartis is requesting a priority review. Since this application proposes a labeling change pursuant to a report on a pediatric study, this application will have a priority review.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Vaishali Jarral	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Suzanne Demko		Y
Clinical	Reviewer:	Martha Donoghue	Y
	TL:	Suzanne Demko	Y
Social Scientist Review (for OTC products)	Reviewer:	NA	

	TL:	NA	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	NA	
	TL:	NA	

Clinical Pharmacology	Reviewer:	Jian Wang	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Yuan Weishi	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrew McDougal	Y
	TL:	Andrew McDougal (acting)	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Sue Ching Lin	Y
	TL:	Liang Zhou	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Steven Donald	N
	TL:	NA	
CMC Labeling Review	Reviewer:	NA	
	TL:	NA	
Facility Review/Inspection	Reviewer:	Mahesh Ramanandham	Y
	TL:	Mahesh Ramanandham	Y
OSE/DMEPA (proprietary name)	Reviewer:	James Shcllick	Y
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Suzanne Robottom	Y
	TL:	Cynthia LaCavita	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	
	TL:	NA	

Bioresearch Monitoring (OSI)	Reviewer:	NA	
	TL:	NA	
Controlled Substance Staff (CSS)	Reviewer:	NA	
	TL:	NA	
Other reviewers	Patient Labeling Reviewer: Sharon Mills DPP: Carole Broadnax - professional reviewer Karen Munoz - consumer reviewer		Y N N
Other attendees ONDQA Biopharmaceutics ONDQA Biopharmaceutics (TL) ONDQA- Pharmaceutical Assessment Chief	Kareen Riviere Sandra Suarez Sarah Miksinski Pope		Y N Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: No Comments</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<p>Comments: Review issues for 60-day letter</p>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: OSI and DOP2 together made an assessment that since this is not an NME, the inspections are not needed.</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? 	<input type="checkbox"/> YES

<p>Comments</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<p>Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason: Not an original NME <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> </p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO Found in the YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Patricia Keegan	
Comments: The pediatric exclusivity determination will be discussed/finalized during the July 10, 2012 Pediatric Exclusivity Board meeting.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74

<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input checked="" type="checkbox"/>	Other <ul style="list-style-type: none"> • Information request to Novartis via email • Request pediatric exclusivity board to reschedule the board meeting to July 10, 2012 from July 31, 2102. • Pharmacology toxicology might have a review issue- RPM will do a follow-up by April 10, 2012 • DMEPA will have comments (re: labeling) in 74-day letter • ONDQA will have comments (re: name/dosage form) in 74-day letter

Vaishali Jarral

Regulatory Project Manager

Date

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval

of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

VAISHALI JARRAL
05/15/2012

KAREN D JONES
05/16/2012

Division of Oncology Products 2

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 203985/0

Name of Drug: Afinitor Disperz (everolimus) Tablets
Strengths- 2mg, 3mg and 5mg.

Applicant: Novartis Pharmaceuticals Corporation

Labeling Reviewed

Submission Date: Feb 29, 2012

Receipt Date: Feb 29, 2012

Background and Summary Description: On February 29, 2012, DOP2 received a new NDA from Novartis for Afinitor Disperz (everolimus) that contains a new dosage form, tablets for oral suspension (which the company described as [REDACTED] ^{(b) (4)} for treatment of patients with TSC who have SEGA and require therapeutic intervention but are not likely to be cured by surgery. This NDA was submitted to fulfill a Pediatric Written Request and as such contains a request for pediatric exclusivity determination. Novartis has submitted the proposed Prescribing Information in doc format as well as in SPL format. In addition, the sponsor has submitted an annotated label to facilitate the labeling discussion.

This review provides a list of formatting revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified:

1. **General Comments:**
 - a. Identifying numbers must precede the heading or subheading by at least two square em's (i.e., two squares of the size of the letter "m" in 8 point type) [see 21 CFR 201.57(d)(7)].
 - b. Use command language throughout the label.

2. Highlights of Prescribing Information Section:

- a. Use command language (e.g., use “Do not use” instead of “should not be used.”). Please refer to 1(b).
- b. HL must be one-half page or less than one-half page [See 21 CFR 201.57(d)(8)].
- c. If the Highlights and Table of Contents do not fit in one page, insert the Table of Contents on page 2 of the labeling.
- d. Under Recent Major Changes, the heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. You have identified the date only once. Please identify the date individually for each heading/subheading See 21 CFR 201.57(a)(5)].

3. Full Prescribing Information (FPI):

- a. Each subheading within a section must be indented and not bolded. (e.g section 2).
- b. Include only references that are important to the prescriber under Section 15. [See 21 CFR 201.57(c)(16)].
- c. Section 17 must reference any FDA-approved patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling)” should appear at the beginning of Section 17 to give it prominence
- d. Manufacturer information is required in labeling (see 21 CFR 201.1 and 201.100(e) for drugs and 21 CFR 610 - Subpart G for biologics) and should be located after the Patient Counseling Information section, at the end of labeling. If the FDA-approved patient labeling is a separate document or is to be detached and distributed to patients, the manufacturer information should be located both after the Patient Counseling Information section and after the FDA-approved patient labeling

Patient Information:

No comments

Recommendations

Novartis Pharmaceuticals Corporation should address the identified deficiencies/ issues and resubmit labeling.

Vaishali Jarral	3/23/12
Regulatory Project Manager	Date
<hr/>	
Chief, Project Management Staff	Date

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- NO** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: DOP2 will request for the waiver in 74-day letter.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
---------	-------------------

Selected Requirements of Prescribing Information (SRPI)

• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

- YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

- YES** 10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

- YES** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

- N/A** 12. All text must be **bolded**.

Selected Requirements of Prescribing Information (SRPI)

Comment:

- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- YES** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- YES** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- NO** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment: *Under Recent Major Changes, the heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (Month/Year) on which the change was incorporated in labeling. Novartis has identified the date only once. DOP2 is going to request sponsor to identify the date individually for each heading/subheading.*

- YES** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *The Previous RMCs were incorporated in the label on 5/2011. This section should be removed if the label is finalized after May 11, 2012.*

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use

Selected Requirements of Prescribing Information (SRPI)

8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- YES** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information (SRPI)

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *The following comment will be conveyed to the sponsor via 74-day letter-Section 17 must reference any FDA-approved patient labeling:*

The statement “see FDA-approved patient labeling (insert type of patient labeling)” should appear at the beginning of section 17 to give it prominence.

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

/s/

VAISHALI JARRAL
05/04/2012

KAREN D JONES
05/04/2012