

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203985Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203985

SUPPL #

HFD #

Trade Name Afinitor Disperz

Generic Name everolimus

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The new dosage form, Afinitor Disperz (everolimus tablets for oral suspension), submitted under NDA 203985 was supported by the following Bioavailability studies: Studies CRAD001X2105 [Study X2105] and CRAD001X2106 [Study X2106]. Study X2105 was a randomized, open label crossover BE study (one 5mg tablet for oral suspension vs. five 1 mg tablets for oral use (market formulation)). Study X2106 was a randomized, open label crossover BE study (one 5mg tablet for oral suspension vs. one 5 mg tablet for oral use (market formulation)).

If it is a supplement requiring the review of clinical data but it is not an effectiveness

supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

The sponsor requested Pediatric Exclusivity which would attach additional 6 months. See item (e) below.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No. The approval of NDA 203985 was not dependent on the results of the studies submitted in response to the pediatric written request. The following clinical investigations studies were submitted in response to the pediatric writted request:

Investigation #1- Study CRAD001M2301

Investigation #2- Updated long-term follow-up data and clinical study report from Study CRAD001C2485

Please note that the studies mentioned above were not essential to the approval of NDA 203985.

Additional information: The pediatric exclusivity board granted exclusivity for this product under this NDA 203985 on July 10, 2012. The division notified the sponsor on July 12, 2012 per the request of the board.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA# 22334 Afinitor (everolimus) Tablets

NDA# NDA# 21560 Zortress (everolimus) Tablets

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

The purpose of this application was to support a new dosage form, Afinitor Disperz (everolimus tablets for oral suspension). Data which support approval of the new dosage form are the two single-dose bioavailability studies conducted in healthy volunteers comparing the approved dosage form Afinitor (everolimus) tablets for oral use with the new dosage form, Afinitor Disperz (everolimus tablets for oral suspension). Please refer to 1c above. Even though the NDA application included clinical investigational studies submitted to fulfill the pediatric written request, those studies were not 'essential to the approval' of

the new dosage form.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug

product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====
Name of person completing form: Vaishali Jarral
Title: Regulatory Project Manager, Division of Oncology Products 2
Date: August 27, 2012

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, Division of Oncology Products 2

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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
08/29/2012

PATRICIA KEEGAN
09/05/2012

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 203985/0 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Oncology Products 2 PDUFA Goal Date: August 29, 2012 Stamp Date: 2/29/2012

Proprietary Name: Afinitor Disperz

Established/Generic Name: Everolimus (tablets for oral suspension)

Dosage Form: Tablets for oral suspension

Applicant/Sponsor: Novartis Pharmaceuticlas Corporation

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): _____
(Attach a completed Pediatric Page for each indication in current application.)

Indication: pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

| |
|---|
| Section A: Fully Waived Studies (for all pediatric age groups) |
|---|

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

| | | Reason (see below for further detail): | | | | | |
|--------------------------|---------|--|---------------|---------------------------|---|------------------------------------|---------------------------------|
| | | minimum | maximum | Not feasible [#] | Not meaningful therapeutic benefit [*] | Ineffective or unsafe [†] | Formulation failed ^Δ |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

| Deferrals (for each or all age groups): | | | | Reason for Deferral | | | Applicant Certification † |
|---|---------------------------|---------------|---------------|------------------------------|---|---|---------------------------|
| Population | | minimum | maximum | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Populations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Date studies are due (mm/dd/yy): _____ | | | | | | | |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

| Pediatric subpopulation(s) in which studies have been completed (check below): | | | | | |
|--|------------------------------|---------------|---------------|---|-----------------------------|
| Population | | minimum | maximum | PeRC Pediatric Assessment form attached?. | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

| Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed: | | | | | |
|--|------------------------------|---------------|---------------|--|--|
| Population | | minimum | maximum | | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | | |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | | |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

| Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations: | | | | | |
|---|------------------------------|---------------|---------------|--------------------------|--------------------------|
| Population | | minimum | maximum | Extrapolated from: | |
| | | | | Adult Studies? | Other Pediatric Studies? |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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
08/27/2012

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA: 4/1/2010

Application Written Request was made to: NDA 22-334

Timeframe Noted in Written Request for Submission of Studies: on or before 6/30/2013

NDA #: 203985 Supplement #: 0

Sponsor: Novartis Pharmaceuticals Corporation

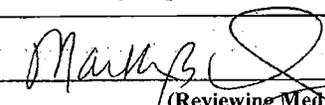
Generic/Non-proprietary Name: everolimus Tradename: Afinitor/Afinitor Disperz

Strength Afinitor: 2.5 mg, 5 mg, 7.5 mg, and 10 mg Afinitor Disperz: 2 mg, 3 mg, 5 mg Dosage Form/Route: Afinitor: tablets
Afinitor Disperz: tablets for oral suspension

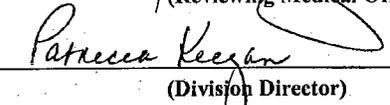
Date of Receipt of Reports of Studies: 2/29/2012

Pediatric Exclusivity Determination Due Date: (180 days from the date of studies receipt): 8/27/12

| | | |
|---|---------------------------------------|----------------------------|
| Was a formal Written Request made for the pediatric studies submitted? | Y <input checked="" type="checkbox"/> | N <input type="checkbox"/> |
| Were the studies submitted after the Written Request? | Y <input checked="" type="checkbox"/> | N <input type="checkbox"/> |
| Were the reports submitted as a supplement or amendment to an NDA/BLA, or original NDA/BLA? | Y <input checked="" type="checkbox"/> | N <input type="checkbox"/> |
| Was the timeframe noted in the Written Request for submission of studies met? | Y <input checked="" type="checkbox"/> | N <input type="checkbox"/> |
| Were the studies reported in accordance with the requirements for filing? (If No, then the next two questions may not apply and should remain unanswered) | Y <input checked="" type="checkbox"/> | N <input type="checkbox"/> |
| Were the studies conducted in accordance with commonly accepted scientific principles and protocols? | Y <input checked="" type="checkbox"/> | N <input type="checkbox"/> |
| Did the studies fairly respond to the Written Request? | Y <input checked="" type="checkbox"/> | N <input type="checkbox"/> |

SIGNED 
(Reviewing Medical Officer)

DATE 6/26/2012

SIGNED 
(Division Director)

DATE 6-28-2012

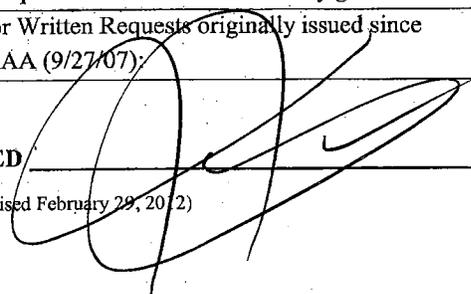
Do not enter in DARRTS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD via Pediatric and Maternal Health Staff PM

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **Granted*** **Denied**

***Additional Information**

| | | |
|--|--|---|
| 1. Pediatric Exclusivity was granted to: | Single Moiety <input checked="" type="checkbox"/> | Combination <input type="checkbox"/> |
| 2. The period of Pediatric Exclusivity granted: | First <input checked="" type="checkbox"/> | Second <input type="checkbox"/> |
| 3. For Written Requests originally issued since FDAAA (9/27/07): | 9 months from the date of this determination is <u>4/10/13</u> | Not Applicable <input type="checkbox"/> |

SIGNED 
(Last revised February 29, 2012)

DATE 7/10/12

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

/s/

MATTHEW A BACHO
07/10/2012

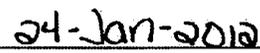
JOHN K JENKINS
07/10/2012

Debarment Certification

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Yanina Gutman, PharmD, RAC
Associate Director, Drug Regulatory Affairs



24-Jan-2012

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|--|---|
| NDA # 203985 BLA # | NDA Supplement # N/A BLA Supplement # | If NDA, Efficacy Supplement Type: N/A |
| Proprietary Name: Afinitor Disperz Established/Proper Name: everolimus Dosage Form: tablets for oral suspension | | Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): |
| RPM: Vaishali Jarral | | Division: DOP2 |
| <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> | | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>August 29, 2012</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) | | <input checked="" type="checkbox"/> None |

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

| | |
|---|---|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p> | <input type="checkbox"/> Received |
| <p>❖ Application Characteristics ³</p> | |
| <p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): Type 3</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input checked="" type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required </p> <p>Comments: Pediatric exclusivity determination was requested from Novartis and granted by Agency under this application.</p> | |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p> | <input type="checkbox"/> Yes, dates |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| <p>❖ Public communications (<i>approvals only</i>)</p> | |
| <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| <ul style="list-style-type: none"> Press Office notified of action (by OEP) | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| <ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated | <input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst |

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| | |
|--|---|
| ❖ Exclusivity | |
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires: Although Afinitor Tablet (different dosage form Afinitor Disperz - both have same sponsor), is considered to be 'same', there is no competitive drug that can be considered to be 'same product' based on the Orphan Drug designation of 'sameness'. |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires: |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires: |
| ❖ Patent Information (NDAs only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input type="checkbox"/> No paragraph III certification Date patent will expire |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

| | |
|--|--|
| <p><i>If "No," continue with question (5).</i></p> <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> |
|--|--|

| |
|-----------------------------------|
| CONTENTS OF ACTION PACKAGE |
|-----------------------------------|

| | |
|---|---|
| ❖ Copy of this Action Package Checklist ⁴ | Included |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |
| Action Letters | |
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Action(s) and date(s) Approval August 29, 2012 |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | August 29, 2012 (final draft from Novartis) |
| • Original applicant-proposed labeling | February 29, 2012 |
| • Example of class labeling, if applicable | |

⁴ Fill in blanks with dates of reviews, letters, etc.

| | |
|---|---|
| <ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | August 29, 2012 for both IFU and PI |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | IFU- April 23, 2012, PI- February 29, 2012 |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |
| <ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | June 22, 2012 |
| <ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i> | May 31, 2102; Acceptability Letter (C. Holquist, OSE) May 31, 2012; Review (J. Schlick, OSE) |
| <ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input checked="" type="checkbox"/> RPM May 4, 2012, Labeling Review (V. Jarral) <input checked="" type="checkbox"/> DMEPA July 13, 2012, Labeling Review (J. Schlick) <input checked="" type="checkbox"/> DMPP/PLT (DRISK) July 24, 2012 <input checked="" type="checkbox"/> ODPD (DDMAC) July 20, 2012, Labeling review (C. Broadnax) <input type="checkbox"/> ODPD (DCPP), July 25, 2012, Labeling Review (K. Munoz) <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews PMHS; July 2, 2012 |
| Administrative / Regulatory Documents | |
| <ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) | May 16, 2012; Filing Review (RPM) <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2) |
| <ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

| | |
|--|--|
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| <ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) | <input checked="" type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) | <input checked="" type="checkbox"/> Verified, statement is acceptable |
| <ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>) | <p>1. August 29, 2012; Approval Letter August 29, 2012; Labeling Negotiations</p> <p>August 28, 2012; Labeling negotitaions (uploaded 8/29/12)</p> <p>August 23, 2012; Labeling Negotiations (uploaded 8/29/12)</p> <p>August 8, 2102; PMC commitments negotiation with Novartis (uploaded 8/10/12)</p> <p>August 1, 2012, Label to Novartis via Email (uploaded 8/07/12)</p> <p>July 25, 2012; IR (Clinical) via Email (uploaded 8/07/12)</p> <p>July 24, 2012, IR (ONDQA and Biopharma), Verbal (infromal meeting)</p> <p>July 19, 2012; IR Letter (CMC) via Mail</p> <p>July 16, 2012; IR (Clinical) via Email (uploaded 7/19/12)</p> <p>July 12, 2012; IR (Clinical) via Email (uploaded 7/19/12)</p> <p>July 12, 2102; Label to Novartis via Email (uploaded 7/19/12)</p> <p>July 12, 2012; Pediatric Exclusivity Granted notification via Email (uploaded 7/12/12)</p> <p>July 5, 2012; IR Letter (CMC) Via Mail</p> |

| | |
|--|--|
| | <p>June 20, 2012; IR Letter (CMC) Via Mail</p> <p>June 19, 2102; IR (Clinical Pharmacology) via Email (uploaded 7/19/12)</p> <p>June 14, 2012; Carton and Container Labeling comments to Novartis via Email (uploaded 6/18/12)</p> <p>June 1, 2012; IR (Clinical) via Email (uploaded 6/4/1212)</p> <p>June 1, 2012; IR (DMEPA) Via Email (uploaded 7/12/12)</p> <p>June 1, 2012; IR (DMEPA) via Email (uploaded 6/4/12)</p> <p>May 11, 2012; Filing Issues Identified Letter via Email (courtesy copy)</p> <p>May 11, 2102; Filing Issues Identified (74-Day letter) via Mail.</p> <p>April 30, 2102; Priority Review Designation letter via Email (courtesy copy-uploaded 6/4/12)</p> <p>April 27, 2012; Priority Review Designation Letter via Mail</p> <p>April 20, 2012, IR via email (Clinical Pharamcology) (uploaded 6/4/12)</p> <p>April 12, 2012; IR via email (Clinical Pharamcology) (uploaded 7/23/12)</p> <p>April 9, 2012; IR via email (CMC and Clinical)- uploaded 4/9/12)</p> <p>April 2, 2012; IR (pediatric exclusivity determination template) via email- uploaded 4/9/12</p> <p>March 23, 2012; IR letter via Email- uploaded 4/9/12)</p> <p>March 21, 2012; IR letter via Mail</p> |
|--|--|

| | |
|--|--|
| | <p>March 19, 2012; IR letter (CMC)</p> <p>March 8, 2012; ACK Letter via Mail</p> <p>March 5, 2012; Email (application orientation meeting details)- uploaded 4/9/12</p> |
| <p>❖ Internal memoranda, telecons, etc.</p> | <p>August 24, 2012; TCON with Novartis (uploaded 8/27/12)</p> <p>July 26, 2012; Wrap-up Meeting (uploaded 8/7/12)</p> <p>July 17, 2012; Team Meeting (uploaded 7/23/12)</p> <p>June 26, 2012; Team Meeting (uploaded 7/23/12)</p> <p>June 13, 2102; Mid-Cycle Meeting (uploaded 7/23/12)</p> <p>May 14, 2012; Team Meeting (uploaded 6/18/12)</p> <p>April 5, 2012; Filing Meeting (uploaded/signed May 16, 2012)</p> <p>March 20, 2012; Internal meeting between OSI and DOP2 (uploaded 4/9/12)</p> <p>March 12, 2012; Planning Meeting (uplaoded March 23, 2012)</p> |
| <p>❖ Minutes of Meetings</p> | |
| <ul style="list-style-type: none"> • Regulatory Briefing (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A or no mtg |
| <ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg September 27, 2011; under IND 66279; Pre-NDA Meeting Minutes issued 10/11/11 <input type="checkbox"/> No mtg September 29, 2009; Under IND 66279; Pre-SNDA Meeting Minutes issued 12/4/12 |
| <ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg October 2, 2007 <input type="checkbox"/> EOP2 Meeting Minutes issued 10/18/07 |
| <ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) | |

| | |
|---|---|
| ❖ Advisory Committee Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| <ul style="list-style-type: none"> Date(s) of Meeting(s) 48-hour alert or minutes, if available (<i>do not include transcript</i>) | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None August 29, 2012; P. Keegan |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None August 15, 2012; S. Demko |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input type="checkbox"/> None Total of two 1) August 6, 2012; ONDQA (PMC) J. Summers 2) August 6, 2012; Biopharmaceutics (PMC); J. Summers |
| Clinical Information⁶ | |
| ❖ Clinical Reviews | |
| <ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) | August 5, 2012; Concurrence in primary clinical review Also see CDTL review above. |
| <ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) | August 5, 2012; Primary Review (Martha Donoghue) |
| <ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | Page 27 of Clinical Review (Dated August 5, 2012) |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> Not applicable |
| ❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | Risk Management plan was submitted by Novartis- Feb 29, 2012 <input type="checkbox"/> None OSE Review; July 24, 2012 (Suzanne Berkman Robottom) |
| ❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) | <input checked="" type="checkbox"/> None requested |

⁶ Filing reviews should be filed with the discipline reviews.

| | | |
|--|--|--|
| Clinical Microbiology | | <input checked="" type="checkbox"/> None |
| ❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review) | | <input type="checkbox"/> None |
| Clinical Microbiology Review(s) (indicate date for each review) | | <input type="checkbox"/> None |
| Biostatistics | | <input type="checkbox"/> None |
| ❖ Statistical Division Director Review(s) (indicate date for each review) | | <input type="checkbox"/> None August 3, 2012; concurrence with primary reviewer |
| Statistical Team Leader Review(s) (indicate date for each review) | | <input type="checkbox"/> None August 3, 2012; concurrence with primary reviewer |
| Statistical Review(s) (indicate date for each review) | | <input type="checkbox"/> None August 3, 2012; primary review(W. Yuan) April 4, 2012; Filing Review (W. Yuan) |
| Clinical Pharmacology | | <input type="checkbox"/> None |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) | | <input type="checkbox"/> None August 7, 2012; concurrence with primary reviewer |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review) | | <input type="checkbox"/> None August 7, 2012; concurrence with primary reviewer |
| Clinical Pharmacology review(s) (indicate date for each review) | | <input type="checkbox"/> None August 7, 2012; primary review(J. Wang) April 5, 2102; Filing Review (J. Wang) |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters) | | <input checked="" type="checkbox"/> None |
| Nonclinical | | <input type="checkbox"/> None |
| ❖ Pharmacology/Toxicology Discipline Reviews | | |
| • ADP/T Review(s) (indicate date for each review) | | <input checked="" type="checkbox"/> None |
| • Supervisory Review(s) (indicate date for each review) | | <input type="checkbox"/> None July 27, 2012; concurrence with primary reviewer |
| • Pharm/tox review(s), including referenced IND reviews (indicate date for each review) | | <input type="checkbox"/> None July 27, 2012; primary review (A. McDougal) April 5, 2102; Filing Review (A. McDougal) |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review) | | <input checked="" type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review) | | <input checked="" type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | | <input checked="" type="checkbox"/> None Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters) | | <input checked="" type="checkbox"/> None requested |

| Product Quality | | <input type="checkbox"/> None |
|--|--|---|
| ❖ Product Quality Discipline Reviews | | |
| <ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> | | <input type="checkbox"/> None |
| <ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> | | <input type="checkbox"/> None August 2, 2012; concurrence with primary reviewer |
| <ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> | | <input type="checkbox"/> None ONDQA August 24, 2012; Memo to the review (S.C.Lin) ONDQA August 2, 2012- Primary Review (S. C. Lin) ONDQA: March 27, 2012; Filing Review (L. Zhou) Biopharmaceutics: August 3, 2012; Final Review (K. Riviere) Biopharmaceutics: March 16, 2012; Filing Review (K. Riviere) |
| ❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i> | | <input type="checkbox"/> Not needed March 22, 2012; Review (S.P. Donald) March 23, 2012; Filing Review (S.P.Donlad) |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> | | <input checked="" type="checkbox"/> None |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | | |
| <input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> | | Included in the final review completed by ONDQA reviewer dated August 2, 2012 |
| <input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i> | | |
| <input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i> | | |
| ❖ Facilities Review/Inspection | | |
| <input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i> | | Date completed: August 23, 2012 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |
| <input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i> | | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> | | <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review) |

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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
09/04/2012

Jarral, Vaishali

From: Jarral, Vaishali
Sent: Wednesday, August 29, 2012 9:33 AM
To: 'Gutman, Nina'
Subject: NDA 203985 Labeling

Importance: High

Attachments: NDA203985_final_Novartis_Labeling_PI_PPI.doc; NDA203985_FINAL_IFU_Novartis_82912.doc

Hello Ms. Gutman,

Please see attached the labeling for NDA 203985. Please submit the final draft labeling to NDA 203985 and NDA 22334/18. Please see FDA's minor edits to section 14.5.



NDA203985_final_Novartis_Label...

Please submit the final draft IFU to NDA 203985.



NDA203985_FINAL_IFU_Novartis_8...

Thanks,
Vaishali

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

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
08/29/2012



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

Memorandum

Date: August 28, 2102
From: Vaishali Jarral, RPM DOP2/OHOP/CDER/FDA
Subject: Teleconference with Novartis Pharmaceuticals Corporation re: NDA 203985

Informal teleconference requested by FDA

Sponsor: Novartis Pharmaceuticals Corporation

NDA: 203985

Drug: Afinitor Disperz (everolimus tablets for oral suspension)

Teleconference Date: August 24, 2012

FDA attendees:

Patricia Keegan (Division Director)

Vaishali Jarral (RPM)

Karen Jones (CPMS)

Tamy Kim (ADRA)

Attending for Novartis Pharmaceuticals Corporation were:

David Lebwohl – Sr. VP and Global Program Head, Afinitor

Gaurav Shah – Sr. Global Clinical Leader

Sara Miao – Clinical Trial Head

Ashdeep Pooni – Senior Clinical Manager

Edwin Schaart – Brand Safety Leader

Frank Grande – Regulatory Liaison, Global Regulatory – CMC

Lynne McGrath – VP, NA Head Drug Regulatory Affairs, Oncology

Joseph Posluszny – Global Program Regulatory Director, Afinitor

Lincy Thomas – Director, Drug Regulatory Affairs

Nina Gutman – Associate Director, Drug Regulatory Affairs

Meeting Summary:

This teleconference was requested by FDA to request the following from Novartis:

- 1) A CBE supplement to NDA 22334 to revise the currently approved SEGA-TSC indication (which was granted under accelerated approval on October 29, 2010 under NDA 22334/S-006) to align with the indication to be approved for Afinitor Disperz under NDA 203985 which will use the same label. Novartis agreed to submit the CBE supplement with the most recent version of the joint Afinitor and Afinitor Disperz label to NDA 22334.

- 2) The formal request for an accelerated approval of NDA 203985 under subpart H. Novartis agreed to FDA's proposal.

Reason for the request: The Indication of SEGA-TSC is under accelerated approval (approved under NDA 22334/S-006 on October 29, 2010) until the confirmatory studies are submitted and reviewed. The clinical data submitted to NDA 203985 do not provide long-term data for efficacy endpoints and therefore are inadequate to convert the accelerated approval to a regular approval.

- 3) A revision to PMC 1917-2 under NDA 203985, removing the sentence indicated below :

“To provide Dissolution Method Development Report and Prior Approval Supplement (including the revised dissolution method and information to support the dissolution acceptance criterion. (b) (4)

FDA assured Novartis that the agency will keep its review commitment but the PMC language should reflect only Novartis' commitment. Novartis agreed to FDA's proposal and agreed to submit the revised PMC to NDA 203985.

Additional discussion during the meeting:

- 4) Novartis asked if FDA is planning to retire NDA 203985. FDA stated that the Agency is not planning to retire this NDA as this is not a type 6 NDA.
- 5) Novartis asked whether FDA will allow the company to submit all documents such as DSURs, PSURs, and annual reports to NDA 22334 with cross reference letters to NDA 203985. FDA recommended that Novartis submit their proposal for consideration by the agency.

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
08/29/2012

Jarral, Vaishali

From: Jarral, Vaishali
Sent: Thursday, August 23, 2012 1:25 PM
To: 'Gutman, Nina'
Subject: NDA 203985- Label

Attachments: IFU_NDA203985_proposed-ifu-to Novartis_82212_notfinal.doc; Afinitor Disperz_label to Novartis- not final_82312.doc

Ms. Gutman,

Please see attached the labeling for NDA 203985. Please note that this is NOT the final version and we will be sending you additional edits in near future.



IFU_NDA203985_pr



Afinitor

posed-ifu-to ... sperz_label to Nova

Thanks,
Vaishali Jarral

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

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
08/29/2012

Jarral, Vaishali

From: Jarral, Vaishali
Sent: Wednesday, August 08, 2012 10:10 AM
To: 'Gutman, Nina'
Subject: PMC milestones and content- NDA 203985

Importance: High

Ms. Gutman,

Please see below the Agency's communication to Novartis regarding Post Marketing Commitments:

Please let me know if you have any concerns or objections re: the content and the milestones by August 10, 2012.

PMC #1

Provide acceptable USP<671> Water Vapor Transmission Rate test (WVTR) results for the proposed commercial packaging system. Provide 3 months accelerated stability data on the first 3 commercial batches post approval when available, to demonstrate comparable stability with that of registration batches.

PMC Schedule Milestones:

Study/Trial Completion:

Final Report Submission: (USP <671> results) 11/30/12

Other: 3 months accelerated stability data 5/31/13

PMC #2

Dissolution Method Development Report and Prior Approval Supplement (including the revised dissolution method and information to support the dissolution acceptance criterion).

PMC Schedule Milestones:

Final Report Submission: 03/29/2013

Other: Prior Approval Supplement

Submission:

08/29/2013

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
08/10/2012

Jarral, Vaishali

From: Jarral, Vaishali
Sent: Wednesday, August 01, 2012 3:07 PM
To: 'Gutman, Nina'
Subject: RE: NDA 203-985 - Afinitor DISPERZ
Importance: High
Attachments: labeling_Novartis_NDA 203985-Aug 12012.doc; Everolimus (AFINITOR DISPERZ IFU_NOVARTIS_AUG 1 2012.doc

Ms. Gutman,

Please see attached the revised Label, PPI and IFU for Afinitor Disperz (NDA 203985). Please note that this is not the final version. We will be sending you more edits in future.

Additional note: Please revert to DOP1 approved label except for the following sections: 1.5, 2.3, 2.4 2.5, 2.6, 5.9, 6.5, 8.4, Paragraph 3 of section 8.7, paragraphs immediately below the structural formula in section 11 and 14.5.

Please submit your revised edits/comments to the label by August 8, 2012.

Thanks,
Vaishali

From: Gutman, Nina [mailto:nina.gutman@novartis.com]
Sent: Tuesday, July 31, 2012 4:20 PM
To: Jarral, Vaishali
Subject: NDA 203-985 - Afinitor DISPERZ

Hi Ms. Jarral,

I am writing to follow-up on the pending NDA for Afinitor DISPERZ.

In case you have not heard, after our meeting last week with the Quality group, Novartis and FDA agreed on two post-approval commitments.

Can you please confirm that there is nothing outstanding at this time?

Also, do you know when we can expect the next iteration of the proposed labeling?

Thanks in advance for your time and feedback.

Nina

Nina Gutman
Regulatory Affairs TA Asc Dir
Novartis Pharmaceuticals Corporation
180 Park Avenue, 105/1W480B

Florham Park, NJ 07932
USA

Cell +1 862 926-8481
Phone +1 862 778-1767
Fax +1 973 781-8265
nina.gutman@novartis.com
www.novartis.com

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

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
08/07/2012

eCTD NDA 203985/0
Afinitor Disperz
Wrap-up Meeting
7-26-12

Date: July 26, 2012

From: Vaishali Jarral, DOP2/OHOP/CDER

Subject: Wrap-up Meeting

| | |
|---------------------------------|--|
| NDA (Original) | 203985/0 |
| Sponsor: | Novartis Pharmaceuticals Corporation |
| Product: | Afinitor Disperz (everolimus) tablets for oral suspension |
| Strengths: | 2mg, 3mg and 5mg |
| Route of Administration: | Oral |
| Submission Date: | February 29, 2012 |
| Received Date: | February 29, 2012 |
| Priority Review: | August 29, 2012 |
| Indication: | Indicated in pediatric and adult patients with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. |

Following Agenda Items were discussed

1. Important Goal Dates were discussed
2. Discipline Specific Reviews of Application: Reviewers opinion about the approvability of this application was discussed
3. Outstanding issues were discussed: Pending reviews, carton and container label, label
4. Discussion of proposed action to Be taken: Approval date, Action Package submission date
5. Labeling Discussion- The edits that were received from Eisai inc to the label were discussed during this meeting.
6. Discussion of sign-off procedure and schedule was discussed
7. Upcoming meetings were discussed- upcoming meetings such as post action feedback meeting.

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
08/07/2012

Jarral, Vaishali

From: Jarral, Vaishali
Sent: Wednesday, July 25, 2012 11:41 AM
To: 'Gutman, Nina'
Subject: NDA 203985; Information Request

Ms.Gutman,

Please see the following clinical comment regarding NDA 203985:

Please provide details regarding the methods used to calculate the median duration of follow-up of patients enrolled in Study M2301 that resulted different proposed values for Section 14.5 of the proposed package insert for Afinitor (9.7 months vs. 8.4 months). Please include the SAS programs/codes used to derive these figures.

Please provide your response to the information request above by COB July 26, 2012.

Thanks,
Vaishali

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
08/07/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 24, 2012
TIME: 10:00AM- 11:00PM (EST)
LOCATION: TCON/CDER WO 2560
APPLICATION: NDA 203985
DRUG NAME: Afinitor
TYPE OF MEETING: FDA initiated TCON
MEETING CHAIR: Kareen Riviera, ONDQA Biopharmaceutics Reviewer
MEETING RECORDER: Jewell Martin, Regulatory Health Project Manager
MEETING PURPOSE: The purpose of the TCON was to discuss an IR sent to Novartis on June 20, 2012 and

FDA Attendees:

Janice Brown, MS, ONDQA CMC Lead
Sue Ching Lin, PhD, ONDQA CMC Reviewer
Sandra Suarez, PhD, ONDQA Biopharmaceutics Reviewer
Kareen Riviera, PhD, ONDQA Biopharmaceutics Reviewer
Vaishali Jarral, MS, Regulatory Health Project Manager
Jewell Martin, MA, MBA, PMP, ONDQA Regulatory Health Project Manager

Novartis Attendees:

Anke Deiderich, Pharmaceutical and Analytical Development, Formulation Expert
Martin Mueller-Zsigmondy, Pharmaceutical and Analytical Develop., Principal Fellow
Peter Kozlik – Pharmaceutical and Analytical Development, Analytical Expert
Nina Gutman – Associate Director, Drug Regulatory Affairs
Joseph Posluszny – Global Program Regulatory Director, Afinitor
Lynne McGrath - VP, NA Head Drug Regulatory Affairs, Oncology
Sheryl Leroy – Franchise Head, Global Regulatory, CMC
Frank Grande – Associate Director, Global Regulatory, CMC
Wing Cheung – Oncology Clinical Pharmacology, Principal Fellow
Olivier Timbal - Pharmaceutical and Analytical Development, Packaging Expert

Meeting notes:

Agreed upon post marketing commitment (PMC):

- The Agency stated that the current dissolution method and acceptance criteria will be accepted on an interim basis. Novartis agreed to submit a dissolution method development report within 4 to 6 months of the action date for the NDA. ^{(b) (4)}



The prior approval supplement should include the revised dissolution method as well as proposed new acceptance criteria with supporting data, e.g.

dissolution data for release and stability batches available at the time of submission.

Packaging system

- Since there is no comparable stability data and USP <671 > test results for the proposed marketing packaging system, the Agency recommends that Novartis use the blister packaging system used in primary stability studies. Additionally Novartis should provide the appropriate 21 CFR Food Additive Regulations citation for the packaging components used in primary stability studies.
 - Novartis explained that they could not use the packaging system used in primary stability studies because the aforementioned packaging system (b) (4). The Agency requested that Novartis to submit a proposal to address USP <671> testing. Novartis agreed to submit by the end of today, July 25, 2012.
- The Agency also requested that Novartis update Module 3 with revised information that was previously submitted on Jul 13, 2012 in Module 1.

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

/s/

JEWELL D MARTIN
07/26/2012

JANICE T BROWN
07/27/2012



NDA 203985

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, PharmD
Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afinitor Disperz (everolimus tablets for oral suspension), 2mg, 3mg, and 5mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by July 24, 2012, in order to continue our evaluation of your NDA.

1. As indicated in your 13-Jul-2012 amendment, the container closure system proposed for marketing is different from that used for the registration stability studies.
 - a. Provide available stability results of the drug product packaged in the proposed commercial container closure system showing comparable stability results with the registration stability data. Refer to Section 2.2.4 of ICH Q1A(R2), which specifies that stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing.
 - b. Provide USP <671> testing results for the proposed commercial blister packaging system. Your 13-Jul-2012 response to Question #1b does not provide sufficient justification for not submitting USP <671> test results in the NDA for the marketing packaging system.
 - c. Conflicting information was provided in Table 1-1 of the amendment regarding the product contact side of the packaging system. The information provided in the original NDA submission shows that (b) (4) (b) (4) are the product contact sides, whereas the 13-Jul-2012 amendment appears to indicate differently. Please clarify.
2. Revise the post-approval stability protocol in Section 3.2.P.8.2 for annual batches. The reduced testing frequency (Table 2-2) that is proposed for the annual batches is not acceptable based on the available stability data. The testing interval should be the same as that for the primary batches (i.e., every (b) (4) months over the first year, every (b) (4) months over the second year, and (b) (4) thereafter through the proposed retest period).

3. The following comments pertain to the Product Element section of SPL that was submitted in the Appendix 8 of the 13-Jul-2012 amendment:
 - a. Revise the established name in the header of the Product Element section to “everolimus tablets for oral suspension.”

4. The following issues pertain to analytical procedure 53501.02 for testing degradation products in the drug product and its validation:
 - a. In Section 3.2.P.5.3, provide linearity data, relative response factors, extraction factors, and limits of detection and quantitation for all the specified degradation products that are included in the drug product specification. It is noted that the data are provided for degradants (b) (4) only.
 - b. Accordingly, revise the calculation formula for degradation products in Section 3.2.P.5.2 based on the relative response factors and extraction factors obtained above.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

JANICE T BROWN

07/19/2012

Janice Brown for Sarah Pope Miksinski, Ph.D.

**Team Meeting
July 17, 2102**

NDA (Original) 203985/0
Sponsor: Novartis Pharmaceuticals Corporation
Product: Afinitor Disperz (everolimus) tablets for oral suspension
Strengths: 2mg, 3mg and 5mg
Route of Administration: Oral
Submission Date: February 29, 2012
Received Date: February 29, 2012
Priority Review: August 29, 2012
Indication: AFINITOR[®] and AFINITOR[®] DISPERZ are indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected

Current Review Team

Director:
Patricia Keegan

Toxicology:
Andrew McDougal

Regulatory:
Vaishali Jarral

Product:
Sue Ching Lin
Liang Zhou (TL)

Clinical:
Martha Donoghue
Suzanne Demko (TL and CDTL)

Statistical:
Weishi Yuan
Kun He (TL)

Clinical Pharmacology:
Jiang Wang
Hong Zhao (TL)

BioPharmaceuticals:
Kareen Riviere
Sandra Suarez (TL)

Consults:

- | | | |
|----|---------------------------------|---|
| a. | DDMAC Reviewer | Carole Broadnax - professional reviewer, Karen Munoz - consumer reviewer |
| b. | DSI Reviewer | Not needed |
| c. | Patient Labeling Reviewer | Sharon Mills |
| d. | OSE/DRISK (RMP) | Suzanne Robottom (Cynthia LaCavita, TL) |
| e. | DMEPA (Carton container and PI) | James Schlick (Todd Bridges, TL) |
| f. | Maternal Health | As needed |
| g. | Facility Reviewer | Mahesh Ramanandham |
| h. | Microbiology Consult | Steven Donald |

- i. Pediatric Page/Perc Review; Doesn't trigger PREA (orphan status)
- j. DPV Bob Pratt
- k. DEPI Cunlin Wang

Team Meeting was held to discuss any pending issues/IRs, need for PMCs/PMRs, review status and facility inspection updates.

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
07/23/2012

From: Jarral, Vaishali
Sent: Monday, July 16, 2012 10:23 AM
To: 'Gutman, Nina'
Subject: NDA 203985- Information Request
Ms. Gutman,

Please provide a response to the comment below regarding NDA 203985 by July 16, 2012:

The Summary of Clinical Safety, submitted as part of the 90-day safety update on May 4, 2012, indicates that 61 of the 76 patients who had been randomized to receive everolimus and who were eligible to continue everolimus during the open label period had an evaluation recorded in the open-label period prior to the July 18, 2011 cutoff date. Please confirm that the remaining 15 patients elected to continue everolimus therapy during the open-label period, or indicate if this information was unknown at the time of data cutoff.

Thank you,
Vaishali

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
07/19/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

From: Jarral, Vaishali
Sent: Thursday, July 12, 2012 3:22 PM
To: 'Gutman, Nina'
Subject: Information request-NDA 203985
Sensitivity: Confidential

Hello Ms. Gutman,

Please provide case report form and/or narratives that describe the adverse event of intentional self-injury for patient 0500_00002 in study M2301 by July 19, 2102. Please also submit your response to NDA 203985.

Thanks,

Vaishali Jarral

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
07/19/2012

From: Jarral, Vaishali
Sent: Thursday, July 12, 2012 10:26 AM
To: 'Gutman, Nina'
Subject: NDA 203985

Attachments: substantial complete label_NDA 203985.doc; edits_7812.ifu.doc
Hello Ms. Gutman,

Please see attached the labeling for NDA 203985 (Afinitor Disperz).

Please send me your proposed edits/comments by July 19, 2012. Please send me via email and via formal submission- annotated label, clean label and tracked label.

Please update this label as needed to maintain the consistency between the different indications. Also note that these are not our final edits to your label.

Thanks,
Vaishali Jarral
301-796-4248



substantial
omplete label_NDA.



edits_7812.ifu.doc
(1 MB)

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

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
07/19/2012



NDA 203985

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, PharmD
Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afinitor Disperz (everolimus tablets for oral suspension), 2mg, 3mg, and 5mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a written response by July 13, 2012, in order to continue our evaluation of your NDA.

1. The following comments pertain to the container closure system (Section 3.2.P.7):
 - a. Provide assurance of safety of all packaging components for the final drug product (as listed in Table 1-1 of Section 3.2.P.7) by reference to appropriate 21CFR food additive regulations.
 - b. Provide USP <671> testing results for the blister packaging system.
 - c. Provide materials of construction and appropriate 21CFR food additive regulations for the container closure system used to package the solid dispersion and the bulk tablets. It is noted that the manufacturing of the solid dispersion, the bulk tablets, and the packaging of the final drug product are performed at different facilities. A container closure system for the transportation of bulk drug products to contract packagers should be described in the application per Section VI.B of the FDA "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics."
2. The following comments pertain to the bulk tablets:
 - a. Provide stability data to demonstrate that the bulk tablets are stable in the proposed containers during the transportation from the manufacturing site in Switzerland to (b) (4) in (b) (4)
 - b. Provide the time limit between the production of the bulk tablets and the packaging of the tablets into blisters. Revise Section 3.2.P.3.3 accordingly.
3. Clarify whether glass or plastic oral syringe was used in the compatibility (in-use) study in Section 3.2.P.8.3.

4. Provide information for Afinitor Disperz in the Product Data Element section of the Structured Product Labeling (SPL). It is noted that this section only contains Product Data information for Afinitor tablets but not for Afinitor Disperz.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

JANICE T BROWN
07/05/2012

**Team Meeting
June 26, 2012**

NDA (Original) 203985/0
Sponsor: Novartis Pharmaceuticals Corporation
Product: Afinitor Disperz (everolimus tablets for oral suspension)
Strengths: 2mg, 3mg and 5mg
Route of Administration: Oral
Submission Date: February 29, 2012
Received Date: February 29, 2012
Priority Review: August 29, 2012
Indication: AFINITOR® and AFINITOR® DISPERZ are indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected

Current Review Team

Director:
Patricia Keegan

Toxicology:
Andrew McDougal

Regulatory:
Vaishali Jarral

ONDQA/Product:
Sue Ching Lin
Liang Zhou (TL)

Clinical:
Martha Donoghue
Suzanne Demko (TL and CDTL)

Statistical:
Weishi Yuan
Kun He (TL)

Clinical Pharmacology:
Jiang Wang
Hong Zhao (TL)

ONDQA/Biopharmaceuticals:
Kareen Riviere
Sandra Suarez (TL)

Consults

| | | |
|----|----------------------------|---|
| a. | DDMAC Reviewer | Carole Broadnax - professional reviewer, Karen Munoz - consumer reviewer |
| b. | DSI Reviewer | Not needed |
| c. | Patient Labeling Reviewer | Sharon Mills |
| d. | OSE/DRISK (RMP) | Suzanne Robottom (Cynthia LaCavita, TL) |
| e. | DMEPA (Carton container) | James Schlick (Todd Bridges, TL) |
| f. | Maternal Health | As needed |
| g. | Facility Reviewer | Mahesh Ramanandham |
| h. | Microbiology Consult | Steven Donald |
| i. | Pediatric Page/Perc Review | Doesn't trigger PREA (orphan status) |
| j. | DPV | Bob Pratt |
| k. | DEPI | Cunlin Wang |

DISCUSSION POINTS:

Pediatric Exclusivity Board Meeting- [July 10, 2012](#)
Team meeting to prepare/rehearse for the board meeting.

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
07/23/2012



NDA 203985

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, PharmD
Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afinitor Disperz (everolimus tablets for oral suspension) 2mg, 3mg, and 5mg.

We also refer to your February 29, 2012 submission, containing original New Drug Application.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by July 13, 2012, in order to continue our evaluation of your NDA.

1. Your proposed dissolution method is  (b) (4)

2.  (b) (4)

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

JANICE T BROWN

06/20/2012

Janice Brown for Sarah Pope Mikinski, Ph.D.

From: Jarral, Vaishali
Sent: Tuesday, June 19, 2012 9:53 AM
To: 'Gutman, Nina'
Subject: Information request- NDA 203985

Hello Ms. Gutman,

Please provide scientific justification for your proposed labeling stating “ (b) (4)


Please provide the relevant dataset and data analyses if available. Please provide your response within 3 business days.

Thank you,
Vaishali

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
07/19/2012

From: Jarral, Vaishali
Sent: Thursday, June 14, 2012 4:06 PM
To: 'Gutman, Nina'
Subject: Carton and Container Labeling for NDA 203985

Attachments: afinitor-disperz-2mg-blistercard-novartis.pdf;
afinitor-disperz-2mg-tradecarton-28s-Novartis.pdf

Please see attached FDA's comments regarding carton and container labeling for NDA 203985.
Please send us the revised carton and container by June 22.



afinitor-disperz-2mgafinitor-disperz-2mg
-blisterca... -tradecart...



Thanks,
Vaishali

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

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
06/18/2012

**Mid-Cycle Meeting
June 13, 2012**

NDA (Original) 203985/0
Sponsor: Novartis Pharmaceuticals Corporation
Product: Afinitor Disperz (everolimus) tablets for oral suspension
Strengths: 2mg, 3mg and 5mg
Route of Administration: Oral
Submission Date: February 29, 2012
Received Date: February 29, 2012
Priority Review: August 29, 2012
Indication: 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.

Current Review Team

Director:
Patricia Keegan

Toxicology:
Andrew McDougal

Regulatory:
Vaishali Jarral

ONDQA/Product:
Sue Ching Lin
Liang Zhou (TL)

Clinical:
Martha Donoghue
Suzanne Demko (TL and CDTL)

Statistical:
Weishi Yuan
Kun He (TL)

Clinical Pharmacology:
Jiang Wang
Hong Zhao (TL)

ONDQA/Biopharmaceuticals:
Kareen Riviere
Sandra Suarez (TL)

Consults

| | | |
|----|----------------------------|---|
| a. | DDMAC Reviewer | Carole Broadnax - professional reviewer, Karen Munoz - consumer reviewer |
| b. | DSI Reviewer | Not needed |
| c. | Patient Labeling Reviewer | Sharon Mills |
| d. | OSE/DRISK (RMP) | Suzanne Robottom (Cynthia LaCavita, TL) |
| e. | DMEPA (Carton container) | James Schlick (Todd Bridges, TL) |
| f. | Maternal Health | As needed |
| g. | Facility Reviewer | Mahesh Ramanandham |
| h. | Microbiology Consult | Steven Donald |
| i. | Pediatric Page/Perc Review | Doesn't trigger PREA (orphan status) |
| j. | DPV | Bob Pratt |
| k. | DEPI | Cunlin Wang |

DISCUSSION POINTS:

- 1) Consultant review updates
- 2) Facility inspection & EER updates
- 3) Confirm the decision that was made regarding need for an Advisory Committee meeting
- 4) RMP, postmarketing requirements (PMRs), and postmarketing commitments (PMCs)
- 5) Determination of what to convey to applicant with regard to identified key deficiencies and the need for additional information
- 6) Labeling issues

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
07/23/2012

From: Jarral, Vaishali
Sent: Friday, June 01, 2012 4:50 PM
To: 'Gutman, Nina'
Subject: NDA 203985
Ms. Gutman,

Please indicate if you plan on marketing physician samples for Afinitor Disperz. During our review, we noticed that there is only one submitted graphic for [REDACTED] (b) (4) [REDACTED]

[REDACTED] status in the FDA database.

Please provide me with your response via email by June 5, 2012.

Please also submit your response as an amendment to NDA 203985.

Thanks,
Vaishali

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
07/12/2012

From: Jarral, Vaishali
Sent: Friday, June 01, 2012 4:55 PM
To: 'Gutman, Nina'
Subject: NDA 203985

Attachments: Picture (Enhanced Metafile)
Hello Ms. Gutman,

Please provide the following information regarding the proposed labeling changes to Section 14.4 of the Afinitor label (excerpted below) :



(b) (4)

1. Please provide a listing of patients (by identification number) meeting the criteria for a greater than 50% reduction in tumor volume of their largest SEGA lesion at six months (referred to in the first sentence in the above paragraph).
2. Please confirm that the nine patients referred to in the second sentence (with DOR ranging from 97 days to 1191 days) are the same nine patients referred to in the first sentence.
2. Please provide the identification numbers of the 8 patients with ongoing volumetric reduction of greater than 50% at the new data cut-off. Are the previous 7 patients included in this group?
3. Please provide variable names used to identify the above patients and the SAS program that used to calculate the duration of response for this subgroup.

Please provide your response by June 8, 2012. Please let me know if that is not possible.
Thank you!
Vaishali Jarral

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
06/04/2012

From: Jarral, Vaishali
Sent: Friday, June 01, 2012 1:16 PM
To: 'Gutman, Nina'
Subject: NDA 203985- Information Request
Hello Ms. Gutman,

Please submit all errors, complaints, and issues Novartis had with respect to the preparation and administration of the suspension in an oral syringe during the phase III trial conducted in patients with TSC with SEGA, irrespective of age.

Please email me the information requested by June 7, 2012.
Please also submit the information to NDA.

Thanks,
Vaishali

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
06/04/2012



NDA 203985

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Yanina Gutman, PharmD
Associate Director

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) dated February 29, 2012, received February 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Everolimus Tablets for Oral Suspension, 2 mg, 3 mg and 5 mg.

We also refer to your March 2, 2012, correspondence, received March 2, 2012, requesting review of your proposed proprietary name, Afinitor Disperz. We have completed our review of the proposed proprietary name, Afinitor Disperz and have concluded that it is acceptable.

The proposed proprietary name, Afinitor Disperz, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 2, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Vaishali Jarral at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
05/31/2012

NDA 203985/0
Afinitor (b) (4) (Afinitor DISPERZ)
Team Meeting
5-14-12

Date: May 14, 2012

From: Vaishali Jarral, DOP2/OHOP/CDER

| | |
|---------------------------------|---|
| NDA (Original) | 203985/0 |
| Sponsor: | Novartis Pharmaceuticals Corporation |
| Product: | Afinitor Disperz (everolimus) tablets, for oral suspension |
| Strengths: | 2mg, 3mg and 5mg |
| Route of Administration: | Oral |
| Submission Date: | February 29, 2012 |
| Received Date: | February 29, 2012 |
| Filing Date: | April 27, 2012 (April 29 is Sunday) |
| Priority Review: | August 29, 2012 |
| Indication: | 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. |

Current Review Team

Director:
Patricia Keegan

Toxicology:
Andrew McDougal

Regulatory:
Vaishali Jarral

Product:
Sue Ching Lin
Liang Zhou (TL)

Clinical:
Martha Donoghue
Suzanne Demko (TL and CDTL)

Statistical:
Weishi Yuan
Kun He (TL)

Clinical Pharmacology:
Jiang Wang
Hong Zhao (TL)

Biopharmaceutical:
Kareen Riviere

Consults:

- | | | |
|----|---------------------------|---|
| a. | DDMAC Reviewer | Carole Broadnax - professional reviewer, Karen Munoz - consumer reviewer |
| b. | Patient Labeling Reviewer | Sharon Mills |

| | | |
|----|---------------------------------|---|
| c. | OSE/DRISK (RMP) | Suzanne Robottom (Cynthia LaCavita, TL) |
| d. | DMEPA (Carton container and PI) | Jim Schlick (Todd Bridges, TL) |
| e. | Maternal Health: | As needed |
| f. | Facility Reviewers: | Mahesh Ramanandham |
| g. | Microbiology Consult: | Steven Donalds |
| h. | Pediatric Page/Perc Review; | Doesn't trigger PREA (orphan status) |
| i. | DPV | Bob Pratt |
| j. | DEPI | Cunlin Wang |

Agenda Items:

1. Upcoming Internal Team Meetings:

Mid-cycle Meeting: May 31, 2102 (agenda was discussed during this team meeting)

Labeling Meetings: Starting from June 11, 2012

Pediatric Exclusivity Board Meeting- July 10, 2012

2. Send proposed **labeling/PMR/PMC/REMS** to applicant: August 8, 2012 (as per the review planner). Are there any PMRs/PMCs to discuss?

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
06/18/2012

From: Jarral, Vaishali
Sent: Friday, May 11, 2012 4:34 PM
To: 'Gutman, Nina'
Subject: Filing communication, NDA 203985

Attachments: Filing_NDA_203985 (vj).pdf
Hello Ms. Gutman,

Please see attached the filing communication letter attached in this email. You will receive an official copy of this letter via mail as well.



Filing_NDA_203985
(vj).pdf (37...

Thanks,
Vaishali Jarral



NDA 203985

FILING COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gutman:

Please refer to your New Drug Application (NDA) dated February 29, 2012, received February 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afinitor Disperz (everolimus) tablets for oral suspension (2mg, 3mg, and 5mg).

During our filing review of your application, we identified the following potential review issues:

Clinical Pharmacology

1. Please provide information that describes the procedures currently being used to ensure that physicians obtain everolimus trough levels that are accurate. The Zortress website provides information regarding the approved test kit and alternative commercial and central reference labs that perform validated everolimus assays. Although current Afinitor labeling includes instructions for periodic measurement of everolimus levels using a validated assay, there do not appear to be resources for physicians on the Afinitor website.

Labeling

2. The term (b) (4) is not an acceptable dosage form term recognized by the Agency. Revise the drug name from the proposed "AFINITOR (everolimus) (b) (4) (b) (4) to "AFINITOR (everolimus) tablets for oral suspension."
3. Eliminate redundancy and improve readability of the Afinitor label by revising the sections relating to the Tuberous Sclerosis (TSC) and Pancreatic Neuroendocrine Tumors (PNET) indications so that they are consistent with current regulatory requirements and recommendations in the following FDA labeling guidance documents:
 - Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075066.pdf>

- Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>.
- Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format
<http://www.fda.gov/ohrms/dockets/98fr/00d-1306-gdl0002.pdf>
- Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing in Labeling
http://www.abclabs.com/Portals/0/FDAGuidance_DraftDrugInteractionStudies2006.pdf.

4. Using the most recently approved version of the Afinitor label, specifically address the following issues in the sections specified below:

a. Indication and Usage:

Because data indicate that the tablets for oral suspension are not bioequivalent to the currently marketed tablets, add a limitation of use in the Indication and Usage section, restricting the use of the tablets for oral suspension to patients with SEGA which is the only population where therapeutic drug monitoring is routinely performed. In addition, provide a reference to the more detailed information in the Dosage and Administration section [ref: 21CFR 201.57 (6)(c) (2)]. Please see the following example of suggested text for the limitation of use:

- Afinitor (everolimus) tablets for oral suspension are recommended for use only in patients with TSC who require therapeutic intervention for SEGA but are not likely to be cured by surgery. Periodic therapeutic drug monitoring is required [see Dosage and Administration (2.x) and Clinical Pharmacology (12.X)].

b. Dosage and Administration section:

- 1) Please reorder the section so that dosage information precedes the administration information.
- 2) Because all oncologists are familiar with how to calculate body surface area, remove the information regarding the use of the (b) (4).
- 3) Remove the information regarding dispersion of Afinitor tablets for oral administration in water, because there are no data to support the efficacy of this preparation in patients with advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, or TSC with renal angiomyolipoma.

c. Adverse Reactions:

- 1) Throughout subsection 6.4 (Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), include only “adverse reactions” as defined in 21 CFR 201.57(c)(7). Avoid other terms, such as “adverse events” or “treatment-emergent adverse events.”
- 2) Throughout subsection 6.3 (Clinical Trial Experience in Renal Angiomyolipoma with Tuberous Sclerosis Complex) and (subsection 6.4 (Clinical Trial Experience in Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), eliminate the long lists of adverse reactions that follow the adverse reaction tables. For less common adverse reactions that do not appear in adverse reaction tables, include only those clinically relevant adverse reactions for which there is a reasonable basis to believe there is a causal role for Afinitor. Non-serious, low frequency adverse reactions should only be listed if there is strong evidence that the drug caused the event. Refer to 21 CFR 201.57 (c) (7) and the FDA Guidance on the content and formatting of this Section for more information.
- 3) For subsection 6.4 (Clinical Trial Experience in Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), the tables describing adverse reactions and clinically significant laboratory abnormalities observed in the randomized trial (Table 6 and Table 7) are adequate and provide information that is more helpful than the information included in the tables describing the observations in the single arm trial (Table 8 and Table 9). Therefore, eliminate Table 8 and Table 9. Summarize all rare, clinically important relevant adverse reactions that occurred in either trial but do not appear in Table 6 or Table 7 and have a reasonably likelihood of being caused by Afinitor in a short paragraph.
- 4) For subsection 6.4 (Clinical Trial Experience in Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), because it is unlikely that Afinitor played a causal role in adverse reactions that occurred with equal or greater frequency in patients randomized to the placebo arm (such as upper respiratory tract infections and bronchitis), eliminate them from Table 6.

d. Use in Specific Populations:

- 1) Revise subsection 8.4 (Pediatric Use) based on 21 CFR 201.57 (c) (9) (iv). This subsection must cite any limitations in the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug (including the need for dose adjustment based on TDM monitoring). If the requirements

for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection must contain an appropriate statement to communicate this limitation (e.g the "Safety and effectiveness in pediatric patients below the age of six months have not been established").

- 2) In subsection 8.4, include a statement to inform clinicians that the effects of everolimus on long-term growth and pubertal development in pediatric patients are unknown.
 - 3) In subsection 8.4, define the indications that are approved for use in pediatric patients (SEGA) and identify the indications for which the safety and effectiveness have not been established.
 - 4) Revise subsection 8.5 (Geriatric Use) based on 21CFR 201.57 (c) (9) (v) for each indication approved for Afinitor.
- e. References:
Eliminate references 2 - 5 because they are not necessary for the safe and effective use of Afinitor.
- f. General Labeling Comments:
For the sections of the label addressing the safety and effectiveness of Afinitor in the treatment of patients with SEGA or renal angiomyolipoma, use command language when providing instructions for clinicians.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

5. Additionally, during our preliminary review of the submitted labeling, we have identified the following labeling format issues. Using the most recently approved version of the Afinitor label, specifically address the following formatting issues in the sections specified below:

a. General:

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. Highlights of Prescribing Information Section:
- 1) HL must be one-half page or less than one-half page [See 21 CFR 201.57(d)(8)]. Either submit the revised labeling that meets the half-page requirement or request a waiver of the requirement. We will consider your request during labeling discussions.
 - 2) If the Highlights and Table of Contents do not fit on one page, insert the Table of Contents on page 2 of the labeling.
 - 3) 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)].
 - 4) Please insert “**Patient Counseling Information Statement**” as a heading to section 17.
 - 5) We acknowledge your amendment dated April 3, 2102, submitted in response to our March 21, 2012 request, which contains proposed “Instructions for Use” labeling. The addition of this labeling requires that the following verbatim statement appear in the Highlights section: **See 17 for PATIENT COUNSELING INFORMATION and Instructions for Use.**
- c. Full Prescribing Information (FPI):
- 1) Each subheading within a section must be indented and not bolded. (e.g section 2).
 - 2) 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.
 - 3) 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.

We request that you submit revised labeling that addresses these issues by May 25, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), instructions for use, and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), instructions for use, and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted pediatric studies with this application and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

PATRICIA KEEGAN
05/11/2012

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

06/04/2012

This courtesy email was sent to Novartis to communicate the filing letter. The filing letter was also sent via mail.



NDA 203985

FILING COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gutman:

Please refer to your New Drug Application (NDA) dated February 29, 2012, received February 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afinitor Disperz (everolimus) tablets for oral suspension (2mg, 3mg, and 5mg).

During our filing review of your application, we identified the following potential review issues:

Clinical Pharmacology

1. Please provide information that describes the procedures currently being used to ensure that physicians obtain everolimus trough levels that are accurate. The Zortress website provides information regarding the approved test kit and alternative commercial and central reference labs that perform validated everolimus assays. Although current Afinitor labeling includes instructions for periodic measurement of everolimus levels using a validated assay, there do not appear to be resources for physicians on the Afinitor website.

Labeling

2. The term [REDACTED] (b) (4) is not an acceptable dosage form term recognized by the Agency. Revise the drug name from the proposed “AFINITOR (everolimus) [REDACTED] (b) (4) [REDACTED] (b) (4) to “AFINITOR (everolimus) tablets for oral suspension.”
3. Eliminate redundancy and improve readability of the Afinitor label by revising the sections relating to the Tuberous Sclerosis (TSC) and Pancreatic Neuroendocrine Tumors (PNET) indications so that they are consistent with current regulatory requirements and recommendations in the following FDA labeling guidance documents:
 - Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075066.pdf>

- Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf>.
- Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format
<http://www.fda.gov/ohrms/dockets/98fr/00d-1306-gdl0002.pdf>
- Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing in Labeling
http://www.abclabs.com/Portals/0/FDAGuidance_DraftDrugInteractionStudies2006.pdf.

4. Using the most recently approved version of the Afinitor label, specifically address the following issues in the sections specified below:

a. Indication and Usage:

Because data indicate that the tablets for oral suspension are not bioequivalent to the currently marketed tablets, add a limitation of use in the Indication and Usage section, restricting the use of the tablets for oral suspension to patients with SEGA which is the only population where therapeutic drug monitoring is routinely performed. In addition, provide a reference to the more detailed information in the Dosage and Administration section [ref: 21CFR 201.57 (6)(c) (2)]. Please see the following example of suggested text for the limitation of use:

- Afinitor (everolimus) tablets for oral suspension are recommended for use only in patients with TSC who require therapeutic intervention for SEGA but are not likely to be cured by surgery. Periodic therapeutic drug monitoring is required [see Dosage and Administration (2.x) and Clinical Pharmacology (12.X)].

b. Dosage and Administration section:

- 1) Please reorder the section so that dosage information precedes the administration information.
- 2) Because all oncologists are familiar with how to calculate body surface area, remove the information regarding the use of the (b) (4).
- 3) Remove the information regarding dispersion of Afinitor tablets for oral administration in water, because there are no data to support the efficacy of this preparation in patients with advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, or TSC with renal angiomyolipoma.

c. Adverse Reactions:

- 1) Throughout subsection 6.4 (Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), include only “adverse reactions” as defined in 21 CFR 201.57(c)(7). Avoid other terms, such as “adverse events” or “treatment-emergent adverse events.”
- 2) Throughout subsection 6.3 (Clinical Trial Experience in Renal Angiomyolipoma with Tuberous Sclerosis Complex) and (subsection 6.4 (Clinical Trial Experience in Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), eliminate the long lists of adverse reactions that follow the adverse reaction tables. For less common adverse reactions that do not appear in adverse reaction tables, include only those clinically relevant adverse reactions for which there is a reasonable basis to believe there is a causal role for Afinitor. Non-serious, low frequency adverse reactions should only be listed if there is strong evidence that the drug caused the event. Refer to 21 CFR 201.57 (c) (7) and the FDA Guidance on the content and formatting of this Section for more information.
- 3) For subsection 6.4 (Clinical Trial Experience in Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), the tables describing adverse reactions and clinically significant laboratory abnormalities observed in the randomized trial (Table 6 and Table 7) are adequate and provide information that is more helpful than the information included in the tables describing the observations in the single arm trial (Table 8 and Table 9). Therefore, eliminate Table 8 and Table 9. Summarize all rare, clinically important relevant adverse reactions that occurred in either trial but do not appear in Table 6 or Table 7 and have a reasonably likelihood of being caused by Afinitor in a short paragraph.
- 4) For subsection 6.4 (Clinical Trial Experience in Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma), because it is unlikely that Afinitor played a causal role in adverse reactions that occurred with equal or greater frequency in patients randomized to the placebo arm (such as upper respiratory tract infections and bronchitis), eliminate them from Table 6.

d. Use in Specific Populations:

- 1) Revise subsection 8.4 (Pediatric Use) based on 21 CFR 201.57 (c) (9) (iv). This subsection must cite any limitations in the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug (including the need for dose adjustment based on TDM monitoring). If the requirements

for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection must contain an appropriate statement to communicate this limitation (e.g the "Safety and effectiveness in pediatric patients below the age of six months have not been established").

- 2) In subsection 8.4, include a statement to inform clinicians that the effects of everolimus on long-term growth and pubertal development in pediatric patients are unknown.
 - 3) In subsection 8.4, define the indications that are approved for use in pediatric patients (SEGA) and identify the indications for which the safety and effectiveness have not been established.
 - 4) Revise subsection 8.5 (Geriatric Use) based on 21CFR 201.57 (c) (9) (v) for each indication approved for Afinitor.
- e. References:
Eliminate references 2 - 5 because they are not necessary for the safe and effective use of Afinitor.
- f. General Labeling Comments:
For the sections of the label addressing the safety and effectiveness of Afinitor in the treatment of patients with SEGA or renal angiomyolipoma, use command language when providing instructions for clinicians.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

5. Additionally, during our preliminary review of the submitted labeling, we have identified the following labeling format issues. Using the most recently approved version of the Afinitor label, specifically address the following formatting issues in the sections specified below:

- a. General:

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. Highlights of Prescribing Information Section:
- 1) HL must be one-half page or less than one-half page [See 21 CFR 201.57(d)(8)]. Either submit the revised labeling that meets the half-page requirement or request a waiver of the requirement. We will consider your request during labeling discussions.
 - 2) If the Highlights and Table of Contents do not fit on one page, insert the Table of Contents on page 2 of the labeling.
 - 3) 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)].
 - 4) Please insert “**Patient Counseling Information Statement**” as a heading to section 17.
 - 5) We acknowledge your amendment dated April 3, 2102, submitted in response to our March 21, 2012 request, which contains proposed “Instructions for Use” labeling. The addition of this labeling requires that the following verbatim statement appear in the Highlights section: **See 17 for PATIENT COUNSELING INFORMATION and Instructions for Use.**
- c. Full Prescribing Information (FPI):
- 1) Each subheading within a section must be indented and not bolded. (e.g section 2).
 - 2) 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.
 - 3) 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.

We request that you submit revised labeling that addresses these issues by May 25, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), instructions for use, and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), instructions for use, and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted pediatric studies with this application and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

PATRICIA KEEGAN
05/11/2012

Sent: Monday, April 30, 2012 10:55 AM
To: 'Gutman, Nina'
Subject: Priority review designation letter for NDA 203985

Attachments: NDA203985_Priority review determination letter.pdf
Hello Ms. Gutman,

Please see attached the "Priority Review Designation" letter for NDA 203985. This letter will be delivered to you via post as well.

Please confirm the receipt of this email.



NDA203985_Priorit
y review dete...

Thank you,

*Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
CDER/FDA
301-796-4248*



NDA 203985

PRIORITY REVIEW DESIGNATION

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gutman:

Please refer to your New Drug Application (NDA) dated February 29, 2012, received February 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afinitor Disperz (everolimus) tablets for oral suspension, 2mg, 3mg, and 5mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is August 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 8, 2012.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before May 11, 2012.

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Division Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

PATRICIA KEEGAN
04/27/2012

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

06/04/2012

Priority review designation letter was communicated to Novartis via email on April 30, 2012. This letter was also sent via mail.



NDA 203985

PRIORITY REVIEW DESIGNATION

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Gutman:

Please refer to your New Drug Application (NDA) dated February 29, 2012, received February 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afinitor Disperz (everolimus) tablets for oral suspension, 2mg, 3mg, and 5mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is August 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 8, 2012.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before May 11, 2012.

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Division Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

PATRICIA KEEGAN
04/27/2012

NDA 203985/0
Afinitor (b) (4) (Afinitor DISPERZ)
Meeting Agenda
4-25-12

Date: April 23, 2012

From: Vaishali Jarral, DOP2/OHOP/CDER

| | |
|---------------------------------|---|
| NDA (Original) | 203985/0 |
| Sponsor: | Novartis Pharmaceuticals Corporation |
| Product: | Afinitor Disperz (everolimus) (b) (4) (2mg, 3mg, 5mg) |
| Dosage form: | Dispersible tablets |
| Strengths: | 2mg, 3mg and 5mg |
| Route of Administration: | Oral |
| Submission Date: | February 29, 2012 |
| Received Date: | February 29, 2012 |
| Filing Date: | April 27, 2012 (April 29 is Sunday) |
| Priority Review: | August 29, 2012 |
| Indication: | 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. |

Agenda Items:

There was an internal meeting between DOP2, ONDQA and Michael Jones (ORP) to get regulatory advice from ORP regarding NDA 203985. The discussion included topics such as identifying the dosage form, user fee, formulation and proprietary name review.

From: Jarral, Vaishali
Sent: Friday, April 20, 2012 4:01 PM
To: 'Gutman, Nina'
Subject: Information Request - NDA 203985
Ms. Gutman,

Please see the following comment regarding NDA 203985:

"In your dataset named 'nmpkpd.xpt' sent on 04/16/2012, data items "Cavg and Cmin are recorded as either '0' or missing for all patients. Please provide Cavg and Cmin data that were used for your PK-PD analysis. In addition, please include the primary efficacy endpoint (overall response) for each individual patient in nmpkpd.xpt."

Please send me the response back via email by April 24, 2012. Please also submit the response to the NDA.

Thanks,
Vaishali

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
06/04/2012

From: Jarral, Vaishali
Sent: Thursday, April 12, 2012 1:57 PM
To: 'Gutman, Nina'
Subject: NDA 203985- Information request
Please see the information request below regarding NDA 203985:

The Subject Identifiers in the datasets 'aident.xpt' and 'pkpd.xpt' are inconsistent, please clarify and provide guidance to merge the two datasets for further pharmacokinetic and pharmacodynamic analyses. In addition, please submit or provide location of the datasets ('nmpk' and 'nmpkpd') that were used in your population PK and PK-PD analyses with a description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that were excluded from the analyses should be flagged and maintained in the datasets.

Please send me your response by April 16, 2012.

Thanks,
Vaishali Jarral

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

07/23/2012

This Information Request was sent via email on April 12, 2102.

The following email was sent to Novartis re: NDA 203985 on April 9, 2012:

From: Jarral, Vaishali
Sent: Monday, April 09, 2012 10:04 AM
To: 'Gutman, Nina'
Subject: NDA 203985- Information Request

Hello Ms. Gutman,

Please provide the following information or direct us to the location of this information in your submission to NDA 203985:

1. A side by side quantitative and qualitative comparison of the chemical compositions of the marketed formulation tablets [Afinitor (everolimus) tablets for oral administration] and the pediatric formulation tablets [Afinitor (everolimus) (b) (4)]
[REDACTED]

2. Data to support the proposed methods for preparation of suspensions of the marketed and pediatric tablet formulations in water. We are particularly interested in suspension particle size, uniformity of particle size, and the time required for each formulation to achieve suspension after contact with water under the conditions described in Section 2 of the proposed Afinitor labeling.

3. You state in Section 3.2.P.2 that “stability of RAD001 dispersible tablet dispersion in water was demonstrated for up to one hour at ambient conditions (approximately 20 – 25 °C).” Provide the corresponding in-use stability data with appropriate analytical test method and acceptance criteria. Also, the labeling should clearly indicate that the suspension should be administered within a time limit that is supported by the in-use stability data.

Please provide your response by COB Wednesday (April 11, 2012).

Thank you,
Vaishali Jarral
301-796-4248

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
04/09/2012



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

Memorandum

Date: April 9, 2012
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 203954/0- Internal Meeting minutes for meeting that was held on March 20, 2012 between OSI reviewer and DOP2 clinical reviewer.*

Meeting between OSI and DOP2
Meeting date: March 20, 2012
Purpose- To determine the need for OSI inspection

Meeting Attendees:

Vaishali Jarral, Regulatory Project Manager, DOP2
Martha Donoghue, Medical Officer, DOP2
Luaren Iacono-Connor- OC/OSI/DGCPC/GCPAB

Meeting summary- an informal meeting took place between OSI and DOP2 to consider the need of inspections for application NDA 203985. It was decided that the inspection is not needed for this submission. In addition it was decided that the clinical reviewer of DOP2 will give OSI a list of few of the investigators who enrolled a relatively large number of patients so that OSI can run a quick screen to see if they have had an inspectional-related issues identified within the past few years.

The meeting ended.

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
04/09/2012

NDA 203985/0
Afinitor DISPERZ (everolimus) (b) (4)
Filing and Planning Meeting Agenda
4-5-12

Date: April 5, 2012

From: Vaishali Jarral, DOP2/OHOP/CDER

Subject: Filing and planning meeting

| | |
|---------------------------------|---|
| NDA (Original) | 203985/0 |
| Sponsor: | Novartis Pharmaceuticals Corporation |
| Product: | Afinitor Disperz (everolimus) (b) (4) (2mg, 3mg, 5mg) |
| Dosage form: | Dispersible tablets |
| Strengths: | 2mg, 3mg and 5mg |
| Route of Administration: | Oral |
| Submission Date: | February 29, 2012 |
| Received Date: | February 29, 2012 |
| Filing Date: | April 27, 2012 (April 29 is Sunday) |
| Priority Review: | August 29, 2012 |
| Indication: | 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. |

Current Review Team

Director:
Patricia Keegan

Toxicology:
Andrew McDougal

Regulatory:
Vaishali Jarral
Karen Jones

Product:
Sue Ching Lin
Liang Zhou (TL)

Clinical:
Martha Donoghue
Suzanne Demko (TL and CDTL)

Statistical:
Weishi Yuan
Kun He (TL)

Clinical Pharmacology:
Jiang Wang
Hong Zhao (TL)

ONDQA Biopharmaceutics:
Kareen Riviere
Sandra Suarez Sharp (liaison)

Consults:

| | | |
|----|---------------------------------|---|
| a. | DDMAC Reviewer | Carole Broadnax - professional reviewer, Karen Munoz - consumer reviewer |
| b. | DSI Reviewer | Not needed |
| c. | Patient Labeling Reviewer | Sharon Mills |
| d. | OSE/DRISK (RMP) | Suzanne Robottom (Cynthia LaCavita, TL) |
| e. | DMEPA (Carton container and PI) | Jim Schlick (Todd Bridges, TL) |
| f. | Maternal Health | as needed |
| g. | SEALD | as needed |
| h. | Facility Reviewers | Mahesh Ramanandham |
| i. | Microbiology Consult | Steven Donald |
| j. | BioPharma Consul | Kareen Riviere |
| k. | Pediatric Page/Perc Review | Doesn't trigger PREA (orphan status) |
| l. | DPV | Bob Pratt |
| m. | DEPI | Cunlin Wang |

Agenda Items (meeting is divided in two sessions):

Session 1: Updates from disciplines to determine the filing deficiencies.

Session 2: Planning meeting to go over the review planner and to discuss the pending information requests and issues.

IR regarding:

Pediatric Exclusivity Determination Template

~~~~~

**From:** Jarral, Vaishali

**Sent:** Monday, April 02, 2012 1:44 PM

**To:** 'Gutman, Nina'

**Subject:** RE: FVDRFs for upcoming AOM (Afinitor Disperz)

**Sensitivity:** Confidential

Hello Ms. Gutman,

In order to make a determination on Pediatric Exclusivity under NDA 203985, we need to know if you have "fairly responded" to the Written Request (WR). To help us make that decision, please complete the template below to describe how your data addresses each term in the WR. We have received your annotated WR which was included in your original NDA submission, however, I request you to please use the format that is in the attached instruction sheet.

This information should be submitted in your application by April 13, 2012. If you have any questions, please contact me.

Thank you,  
Vaishali Jarral

## Pediatric Exclusivity Determination Template

The instructions below will help you complete this template. Please remove the italicized text prior to submission with your application. Additionally, if there are differences between the WR and your application, it is helpful to boldface those differences as has been done in the examples below. In addition, please alert the FDA Regulatory Project Manager about any differences between the WR and what is being submitted.

As you progress through the template, please provide detailed information and arrange the template sections to follow the exact order of the WR. And if it is possible, please link the sections of this template to the appropriate parts of your application that contain the relevant material or data under discussion.

The first column is intended to reflect verbatim what is in the final WR, section by section. Some WRs may have sections in a different order, or may include sections not included in this template (i.e., Additional Studies Required section). Please arrange the sections in this template to match the order of your WR.

If the WR has been amended, it is best to incorporate the revisions into the template. A statement that indicates the revisions date (Revised MM/DD/YYYY) should follow the heading for the column. This will save us time when reviewing the appropriate document(s).

| <b>Written Request Items</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>Information Submitted/ Sponsor's response</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Types of studies/ Study Design:</b><br/> <i>This section should list studies exactly as written in the WR</i></p> <p><i>Example:</i><br/> <i>Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.</i></p> <p><i>Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.</i></p> | <p><b>Types of studies:</b><br/> <i>This section should list complete details of the studies actually performed. Please boldface any information that differs from what was specified in the WR.</i></p> <p><i>Example:</i><br/> <i>Study 1: Multi-center, randomized, placebo controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.</i></p> <p><i>Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.</i></p> |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Indication(s) to be studied:</b><br/> <i>This section should list the indication(s) exactly as written in the WR.</i></p> <p><i>Example:</i><br/> <i>DRUG for the treatment of the signs and symptoms of disease x.</i></p>                                                                                                                                                                                                                                                                                                                                                   | <p><b>Indication(s) studied:</b><br/> <i>This section should list the indication(s) of the studies actually performed.</i></p> <p><i>Example:</i><br/> <i>DRUG for the treatment of the signs and symptoms of disease x.</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>Written Request Items</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <p><b>Information Submitted/ Sponsor's response</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>Age group and population in which study will be performed:</b><br/> <i>This section should list the age group and population exactly as written in the WR.</i></p> <p><i>Example:</i><br/> <i>Study 1: Study should enroll patients aged X to Y years. Should enroll pediatric patients approximately evenly distributed among the following age groups: 2 to &lt;6 years, 6 to &lt;12 years, and 12 to 16 years.</i></p> <p><i>Study 2: Study should enroll a sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.</i></p> | <p><b>Age group and population in which study was performed:</b><br/> <i>This section should list the age group and population of the studies actually performed. Please provide the specific breakdown of the pediatric age groups (i.e. number of patients aged birth to 6 months, 7 months to 1 year, etc).</i></p> <p><i>Example:</i><br/> <i>Study 1: The study enrolled patients aged X to, Z years, distributed among the following age groups: 2 to &lt;6 years(X), 6 to &lt;10 years (Z), and 12 to 16 years (Z).</i></p> <p><i>Study 2: The study enrolled Z patients in the following age groups: 2 to &lt;6 years(X), 6 to &lt;12 years (Y), and 12 to 16 years (Z).</i></p> |
| <p><b>Number of patients to be studied or power of study to be achieved:</b><br/> <i>This section should list the minimum number of patients, if any, specified in the WR.</i></p> <p><i>Example:</i><br/> <i>Study 1: The study should include at least X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc)</i></p>                                                                                                                                                                                                                  | <p><b>Number of patients studied or power achieved:</b><br/> <i>This section should list the number of patients in each study separately. In addition, please provide the racial and ethnic breakdown (if specified in the WR), ages of patients (if specified in the WR), and the number of males and females for each study (if specified in the WR).</i></p> <p><i>Example:</i><br/> <i>Study 1: Study1 randomized 500 patients in the (drug name, concentration, form etc) DRUG arm and 500 patients in the comparator arm.</i></p>                                                                                                                                                  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.</i></p> <p><i>Study 2: This study should be powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study should include at least X evaluable patients. .</i></p>                                                                                                                         | <p><i>250 patients in the active arm were female, and <b>249 were less than three years of age.</b></i><br/> <i>245 patients in the placebo arm were females and 260 were less than 3 years.</i></p> <p><i>Study 2: <b>This study was powered to detect a 40% change in drug clearance...</b></i></p>                                                                                                                                                                                                                                                 |
| <p><b>Written Request Items</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p><b>Information Submitted/ Sponsor's response</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p><b>Entry criteria:</b><br/> <i>This section should list the entry requirements as specified in the WR.</i></p> <p><i>Example:</i><br/> <i>Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs</i><br/> <i>Patients must have a negative pregnancy test if female..</i></p>                                                                                                                                                                                    | <p><b>Entry criteria used:</b><br/> <i>This section should list the entry requirements of the studies actually performed. Please boldface any difference between the entry requirements listed in the WR and the study performed.</i></p> <p><i>Example:</i><br/> <i>Pediatric patients with disease x diagnosed by lab tests of LFTs were included.</i><br/> <i>Pregnancy tests were performed on all female patients and were negative</i></p>                                                                                                      |
| <p><b>Clinical endpoints:</b><br/> <i>This section should list the clinical endpoints as specified in the WR.</i></p> <p><i>Example:</i><br/> <i>Study 1: Clinical outcome and safety will be the primary endpoints.</i></p> <p><i>Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.</i></p> | <p><b>Clinical endpoints used:</b><br/> <i>This section should list the clinical endpoints of the studies actually performed. .</i></p> <p><i>Example:</i><br/> <i>Study 1: Clinical outcome assessment of signs and symptoms and safety were the endpoints for this study.</i></p> <p><i>Study 2: Pharmacokinetic parameters were determined from assessments of (drug name, concentration, form etc) DRUG plasma concentration from all study participants. Single dose and steady state AUC, Cmax, Tmax , and CL/F values were determined.</i></p> |
| <p><b>Timing of assessments: if appropriate</b><br/> <i>This section should list any pre-clinical studies and/ or any studies the WR specified be performed prior to a subsequent study.</i></p>                                                                                                                                                                                                                                                                                                      | <p><b>Timing of assessments:</b><br/> <i>This section should list any pre-clinical studies and/ or studies that the WR specified be performed prior to another study (i.e. PK study prior to efficacy study) and the sequence of the studies. Please boldface the studies</i></p>                                                                                                                                                                                                                                                                     |

|                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>Example:</i><br/>Pre-clinical juvenile animal studies in animal-X must be performed and evaluated by the agency to assess the possible occurrence of condition X prior to initiation of studies 1 and 2 in pediatric patients.</p>                                                                                                                                                   | <p>not performed according to the sequence in the WR.</p> <p><i>Example:</i><br/>Juvenile animal studies in animal-X were performed and evaluated by the agency prior to initiation of studies in pediatric patients.</p>                                                                                                                                                                                         |
| <p><b>Written Request Items</b></p>                                                                                                                                                                                                                                                                                                                                                        | <p><b>Information Submitted/ Sponsor's response</b></p>                                                                                                                                                                                                                                                                                                                                                           |
| <p><b>Drug specific safety concerns:</b><br/><i>This section should just include a cut and paste of what is in the section from the WR</i></p> <p><i>Example:</i><br/>There is concern that drugs in this class may lead to safety signal X. Growth and development must be followed for x time. All adverse events must be reported.</p>                                                  | <p><b>Drug specific safety concerns evaluated:</b><br/><i>This section should list any drug safety concerns, along with the specific tests performed to evaluate them.</i></p> <p><i>Example:</i><br/>Clinical laboratory measures to assess toxicity X were performed at baseline and at the end of the treatment period. Growth and development were followed for x time. All adverse events were reported.</p> |
| <p><b>Drug information:</b><br/><i>Cut and paste from the WR</i></p> <p><i>Examples in italics</i></p> <ul style="list-style-type: none"> <li>• <b>Route of administration:</b> <i>Oral</i></li> <li>• <b>Dosage:</b> <i>75 and 50 mg</i></li> <li>• <b>Regimen:</b> <i>list frequency of dosage administration</i></li> <li>• <b>Formulation:</b> <i>disintegrating tablet</i></li> </ul> | <p><b>Drug information:</b></p> <p><i>Examples in italics</i></p> <ul style="list-style-type: none"> <li>• <b>Route of administration:</b> <i>Oral</i></li> <li>• <b>Dosage</b> <i>75 mg,</i></li> <li>• <b>Regimen:</b> <i>Twice daily</i></li> <li>• <b>Formulation:</b> <i>disintegrating tablet</i></li> </ul>                                                                                                |
| <p><b>Statistical information (statistical analyses of the data to be performed):</b><br/><i>This section should list the statistical tests in the WR</i></p> <p><i>Example:</i><br/><i>Study 1 - Study should use the following criteria for non-inferiority:</i></p>                                                                                                                     | <p><b>Statistical information (statistical analyses of the data to be performed):</b><br/><i>This section should list the statistical tests the Sponsor used. List the power of study and statistical assessments.</i></p> <p><i>Example:</i><br/><i>Study 1- Sponsor used a two-sided 95% confidence interval (CI) of</i></p>                                                                                    |

|                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.</i></p> <p><i>Study 2: The pharmacokinetic parameters calculated should be analyzed by descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.</i></p>                                                                                             | <p><i>treatment difference in improvement rates. DRUG was within 25% of the comparator's response rate demonstrating non-inferiority.</i></p> <p><i>Study 2: Descriptive PK data analysis was performed. Effect of covariates age, body weight, gender, on AUC, Vd, t1/2, Cmax, Tmax Css and CI/F were assessed and compared to adults</i></p>                                                                                                    |
| <b>Written Request Items</b>                                                                                                                                                                                                                                                                                                                                                                                                 | <b>Information Submitted/ Sponsor's response</b>                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>Labeling that may result from the studies:</b><br/> <i>Appropriate sections of the label may be changed to incorporate the findings of the studies.</i></p>                                                                                                                                                                                                                                                            | <p><b>Labeling that may result from the studies:</b><br/> <i>Sponsor did/did not submit proposed labeling</i></p>                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Format of reports to be submitted:</b><br/> <i>Verbatim form the WR</i></p> <p><i>Example:</i><br/> <i>Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.</i><br/> ... </p> | <p><b>Format of reports submitted:</b><br/> <i>This is based on what was submitted</i></p> <p><i>Example:</i><br/> <i>Full study reports not previously submitted to the Agency including full analysis, assessment, and interpretation of the data were submitted .The reports included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the WR..</i></p> |
| <p><b>Timeframe for submitting reports of the studies:</b><br/> <i>Specify date in WR</i></p> <p><i>Example:</i><br/> <i>Reports of the above studies must be submitted to the Agency on or before 12/05/01.</i></p>                                                                                                                                                                                                         | <p><b>Timeframe for submitting reports of the studies:</b><br/> <i>The FDA will insert the receipt date here.</i></p>                                                                                                                                                                                                                                                                                                                             |

-----  
**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  
04/09/2012

**From:** Jarral, Vaishali  
**Sent:** Friday, March 23, 2012 9:17 AM  
**To:** 'Gutman, Nina'  
**Subject:** AI Letter- NDA 203985

**Attachments:** nda\_203985\_IR\_Patient Labeling.pdf  
Ms. Gutman,

Please see attached an AI letter for NDA 203985. Please confirm the receipt of this email.

Thank you,  
Vaishali Jarral



nda\_203985\_IR\_Pa  
tient Labeling...



NDA 203985

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Yanina Gutman, Pharm.D.  
Associate Director  
One Health Plaza  
East Hanover, New Jersey 07936-1080

Dear Ms. Gutman,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afinitor Disperz (everolimus) dispersible tablets (2mg, 3mg, and 5mg).

We are reviewing the proposed labeling including patient information, also known as the patient package insert (PPI), in your submission and have the following comments and requests for information regarding the PPI. We request your written response by 04/02/12 in order to continue our evaluation of your NDA.

1. Your proposed PPI has a Flesch Reading Grade Level of 11.9 and a Flesch Reading Ease Level of 29.9. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.
2. The instructions for preparing a dose of suspension with Afinitor Disperz dispersible tablets are included within the body of the PPI and are lengthy. Develop separate "Instructions for Use" (IFU) that will be packaged with the product and given to the patient or caregiver when the product is dispensed, and submit this material to the NDA.
3. Simplify the language in the PPI and IFU to improve the readability scores as described above. In general, use active voice and non-technical language as much as possible in the PPI and IFU.
4. Add the following bullet in the PPI section "How should I take Afinitor?"
  - If your healthcare provider prescribes Afinitor Disperz dispersible tablets for you, see the "Instructions for Use" that comes with your medicine for instructions on how to prepare your dose.

5. We have the following recommendations to assist you in developing the "Instructions for Use:"
- a. Place a header at the top of the document similar to the one at the top of the PPI, but title it "Instructions for Use" instead of "Patient Information."
  - b. Include the same introductory paragraph as in the PPI, but refer to "Instructions for Use" instead of "Patient Information."
  - c. Following the introductory paragraph, provide a list of the supplies needed to prepare the suspension.
  - d. Instructions that are not sequential should be bulleted.
  - e. Instructions that are sequential should be noted as "Step 1, Step 2" etc.
  - f. If instructions should be repeated more than once, do not repeat steps. Refer the reader back to listed steps. For example "Repeat steps 3 to 5".
  - g. Figures (diagrams or photos) should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related step. The diagrams or photos should be labeled as "Figure A, Figure B" etc.
  - h. For devices, there should be a figure which includes detailed labeling for each part of the device with which the patient is expected to become familiar. For example, a syringe should have the plunger labeled and also the numbering and markings on the barrel of the syringe. The numbering and markings should be clearly visible and easy for the patient to read.
  - i. Refer to each figure at the end of each numbered step. For example, at the end of Step 1, say (See Figure A).
  - j. Delete (b) (4) and only use mLs because spoon sizes may vary.
  - k. If the IFU will not be attached to the PPI, include the following at the end of the IFU:
    - (1) Storage instructions exactly as written in the PPI
    - (2) "This Instructions for Use has been approved by the U.S. Food and Drug Administration."
    - (3) Manufacturer's name and address
    - (4) Revised (or Approved for new NDAs or BLAs) Month Year
  - l. If the IFU will be attached to the PPI, include the following at the end of the IFU:
    - (1) "This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration."
    - (2) Manufacturer's name and address
    - (3) Date revised (or date issued for new NDAs or BLAs) Month Year

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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

/s/  
-----

PATRICIA KEEGAN  
03/21/2012

-----  
**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  
04/09/2012



NDA 203985

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Yanina Gutman, Pharm.D.  
Associate Director  
One Health Plaza  
East Hanover, New Jersey 07936-1080

Dear Ms. Gutman,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afinitor Disperz (everolimus) dispersible tablets (2mg, 3mg, and 5mg).

We are reviewing the proposed labeling including patient information, also known as the patient package insert (PPI), in your submission and have the following comments and requests for information regarding the PPI. We request your written response by 04/02/12 in order to continue our evaluation of your NDA.

1. Your proposed PPI has a Flesch Reading Grade Level of 11.9 and a Flesch Reading Ease Level of 29.9. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level.
2. The instructions for preparing a dose of suspension with Afinitor Disperz dispersible tablets are included within the body of the PPI and are lengthy. Develop separate "Instructions for Use" (IFU) that will be packaged with the product and given to the patient or caregiver when the product is dispensed, and submit this material to the NDA.
3. Simplify the language in the PPI and IFU to improve the readability scores as described above. In general, use active voice and non-technical language as much as possible in the PPI and IFU.
4. Add the following bullet in the PPI section "How should I take Afinitor?"
  - If your healthcare provider prescribes Afinitor Disperz dispersible tablets for you, see the "Instructions for Use" that comes with your medicine for instructions on how to prepare your dose.

5. We have the following recommendations to assist you in developing the "Instructions for Use:"
  - a. Place a header at the top of the document similar to the one at the top of the PPI, but title it "Instructions for Use" instead of "Patient Information."
  - b. Include the same introductory paragraph as in the PPI, but refer to "Instructions for Use" instead of "Patient Information."
  - c. Following the introductory paragraph, provide a list of the supplies needed to prepare the suspension.
  - d. Instructions that are not sequential should be bulleted.
  - e. Instructions that are sequential should be noted as "Step 1, Step 2" etc.
  - f. If instructions should be repeated more than once, do not repeat steps. Refer the reader back to listed steps. For example "Repeat steps 3 to 5".
  - g. Figures (diagrams or photos) should accompany all numbered steps as appropriate and should be placed immediately adjacent to the related step. The diagrams or photos should be labeled as "Figure A, Figure B" etc.
  - h. For devices, there should be a figure which includes detailed labeling for each part of the device with which the patient is expected to become familiar. For example, a syringe should have the plunger labeled and also the numbering and markings on the barrel of the syringe. The numbering and markings should be clearly visible and easy for the patient to read.
  - i. Refer to each figure at the end of each numbered step. For example, at the end of Step 1, say (See Figure A).
  - j. Delete (b) (4) measures and only use mLs because spoon sizes may vary.
  - k. If the IFU will not be attached to the PPI, include the following at the end of the IFU:
    - (1) Storage instructions exactly as written in the PPI
    - (2) "This Instructions for Use has been approved by the U.S. Food and Drug Administration."
    - (3) Manufacturer's name and address
    - (4) Revised (or Approved for new NDAs or BLAs) Month Year
  - l. If the IFU will be attached to the PPI, include the following at the end of the IFU:
    - (1) "This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration."
    - (2) Manufacturer's name and address
    - (3) Date revised (or date issued for new NDAs or BLAs) Month Year

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

*{See appended electronic signature page}*

Patricia Keegan, M.D.  
Director  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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

/s/  
-----

PATRICIA KEEGAN  
03/21/2012



NDA 203985

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Yanina Gutman, Pharm.D.  
Associate Director  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Gutman:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afinitor Disperz (everolimus) dispersible tablets (2mg, 3mg, 5mg).

As part of our filing assessment for the Chemistry, Manufacturing and Control section of your submission we have the following comments and information requests. Please submit your written response to your NDA no later than April 16, 2012.

1. There is insufficient data to support the adequacy of the selected dissolution method (e.g. the amount and type of surfactant, sink conditions, and dissolution apparatus are not justified). Additionally, your proposed method is not discriminating because it fails to reject batches that are not bioequivalent (Study X2105 and X2106). Therefore, we have the following recommendations:
  - a. Develop a new dissolution method that is adequate/optimal for your product. For the new method, provide a detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The validation data for the analytical method (precision, accuracy, etc.) and suitability of the proposed dissolution test (robustness, etc.) should also be included in the report;
  - b. Provide the data supporting the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm$  10-20% change to the specification-ranges of these variables) (b) (4)

[REDACTED]

2. Provide the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

*{See appended electronic signature page}*

Sarah C. Pope Miksinski, Ph.D.  
Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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

/s/  
-----

SARAH P MIKSINSKI  
03/19/2012

**NDA 203985/0**  
Afinitor (b) (4) (Afinitor DISPERZ)  
**Planning Meeting Agenda**  
**3-12-12**

**Date:** March 12, 2012  
**From:** Vaishali Jarral, DOP2/OHOP/CDER  
**Subject:** Planning Meeting

---

|                                |                                                                                                                                                                                                         |
|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>NDA (Original)</b>          | <b>203985/0</b>                                                                                                                                                                                         |
| <b>Sponsor:</b>                | Novartis Pharmaceuticals Corporation                                                                                                                                                                    |
| <b>Product:</b>                | Afinitor Disperz (everolimus) (b) (4)<br>(2mg, 3mg, 5mg)                                                                                                                                                |
| <b>Dosage form</b>             | Dispersible tablets                                                                                                                                                                                     |
| <b>Strengths</b>               | 2mg, 3mg and 5mg                                                                                                                                                                                        |
| <b>Route of Administration</b> | Oral                                                                                                                                                                                                    |
| <b>Submission Date:</b>        | February 29, 2012                                                                                                                                                                                       |
| <b>Received Date:</b>          | February 29, 2012                                                                                                                                                                                       |
| <b>Indication:</b>             | 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. |

**Current Review Team**

**Director:**  
Patricia Keegan

**Toxicology:**  
Andrew McDougal

**Regulatory:**  
Vaishali Jarral

**Product:**  
Sue Ching Lin  
Liang Zhou (TL)

**Clinical:**  
Martha Donoghue  
Suzanne Demko (TL and CDTL)

**Statistical:**  
Weishi Yuan  
Kun He (TL)

**Clinical Pharmacology:**  
Jiang Wang  
Hong Zhao (TL)

**Consults:**

- |    |                                 |                                                                             |
|----|---------------------------------|-----------------------------------------------------------------------------|
| a. | DDMAC Reviewer                  | Carole Broadnax - professional reviewer,<br>Karen Munoz - consumer reviewer |
| b. | DSI Reviewer                    | TBD                                                                         |
| c. | Patient Labeling Reviewer       | Sharon Mills                                                                |
| d. | OSE/DRISK (RMP)                 | Suzanne Robottom (Cynthia LaCavita, TL)                                     |
| e. | DMEPA (Carton container and PI) | Jim Schlick (Todd Bridges, TL)                                              |
| f. | Maternal Health:                | As needed                                                                   |
| g. | Facility Reviewers:             | ONDQA RPM will let me know                                                  |
| h. | Microbiology Consult:           | ONDQA RPM will let me know                                                  |
| i. | BioPharma Consult:              | Kareen Riviere                                                              |
| j. | QT-IRT Consult                  | Not needed                                                                  |
| k. | Pediatric Page/Perc Review;     | Doesn't trigger PREA (orphan status)                                        |
| l. | DPV                             | Bob Pratt                                                                   |
| m. | DEPI                            | Cunlin Wang                                                                 |

**Agenda Items:**

1. **Review Status:**
  - a. Priority Review requested (PDUFA date)- August 29, 2012 (Division signature)
  - b. In light of the anticipated approval of the proposed 5-mg dispersible tablet strength, Novartis is seeking a waiver for in-vivo bioavailability studies for the proposed 2-mg and 3-mg dispersible tablets.
  - c. Sponsor is also requesting pediatric Exclusivity determination. (Due date to grant exclusivity is August 27, 2012)
  - d. Pediatric Board Meeting- July 31, 2012
2. **Dates Milestone Letters Must Issue and PDUFA meetings**

| <b>Action</b>                                                | <b>Date</b>    |
|--------------------------------------------------------------|----------------|
| Acknowledgment letter- Issued                                | March 12, 2012 |
| Application Orientation Presentation Meeting                 | April 2, 2012  |
| Filing meeting                                               | April 5, 2012  |
| Inform applicant of review designation, filing determination | April 29, 2012 |
| Deficiencies Identified Letter (74 day letter):              | May 13, 2012   |
| Mid-Cycle Meeting                                            | May 31, 2012   |

|                                                                                                                                                                                                                    |                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Labeling Meetings                                                                                                                                                                                                  | First two weeks of June                                                                                          |
| Begin Labeling and PMC/PMR discussions with applicant                                                                                                                                                              | Review planner date is August 15                                                                                 |
| Complete primary & secondary reviews<br><br>CDTL Review<br>Do we need tertiary reviews?                                                                                                                            | Review planner date is August 5 <sup>th</sup> and 8 <sup>th</sup><br><br>Review planner date is August 15<br>No. |
| Hold Wrap-up meeting                                                                                                                                                                                               | TBD (Mid- July)                                                                                                  |
| Compile and Circulate Action letter and Action Package                                                                                                                                                             | August 15, 2012                                                                                                  |
| Following items must be submitted to the Pediatric Board RPM :<br><ul style="list-style-type: none"> <li>• Annotated WR</li> <li>• Original WR</li> <li>• Proposed Label</li> <li>• Pediatric Checklist</li> </ul> | By July 24, 2012 for July 31 Board meeting                                                                       |
| Pediatric Exclusivity Board Meeting                                                                                                                                                                                | July 31, 2012                                                                                                    |
| Pediatric Exclusivity Determination deadline                                                                                                                                                                       | August 27, 2012                                                                                                  |
| PDUFA Date                                                                                                                                                                                                         | August 29, 2012                                                                                                  |
| Complete DD review and Sign off                                                                                                                                                                                    | August 29, 2012                                                                                                  |

3. **Upcoming Meetings:**

- a. **Applicant Orientation Presentation:** Scheduled for 10:40 AM, April 2, 2012, during OHOP Friday Clinical Rounds.  
The advice document regarding AOP was sent to the sponsor.
- b. **Filing Meeting:** Scheduled for April 5, 2012
- c. **Mid-Cycle Meeting:** May 31, 2012
- d. **Labeling Meetings:** Scheduled for first two weeks of June

- e. **Substantial complete label** to PLT by June 20 (approximate date) with 2 weeks deadline
  - f. **Team Meetings and PMR/PMC Working meetings:** How many meetings would the team prefer? **Discussion: Monthly**
  - g. **Wrap- Up Meeting:** TBD
  - h. **Team meeting to prepare for the Pediatric Board meeting-** To be scheduled
4. **Miscellaneous Items or Issues:**
- a. Do we need a clinical study site Audits?  
**Discussion:** TBD
  - b. Any additional consult review input (such as Qt-IRT )?  
**Discussion:** Division of neurology (might)
  - c. The label has a PPI. Are we ok with the PPI?  
**Discussion:** IR/AI letter will be drafted re: PPI
  - d. Propriety name review process has started
  - e. Will or has Clinical pharmacology/clinical identified any early PMC/PMRs?  
**Discussion:** No, too early in the process.
  - f. Do we need to have teleconference with the Applicant before the filing meeting regarding any outstanding issues?  
**Discussion:** No.
  - g. Jewell Martin will process the following:
    - **Microbiology (in process)**
    - **Establishment (EES) (in process)**
    - **Compliance**
    - **Environmental Assessment**

Action Item:

- 1) ONDQA will draft an AI letter re: CMC issues
- 2) OND will draft an AI letter re: PPI issues

- 3) Internal meeting with pediatric team (might be needed)
- 4) OND RPM to remind the team to bring their interim deliverable and filing review to the fling meeting on April 5, 2012.
- 5) OND RPM will schedule wrap-up and team meetings
- 6) OND RPM will contact OSI to consider the need for site inspection

-----  
**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  
03/23/2012



NDA 203985

**NDA ACKNOWLEDGMENT**

Novartis Pharmaceuticals Corporation  
Attention: Yanina Gutman, Pharm.D.  
Associate Director  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Gutman:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Afinitor Disperz (everolimus) dispersible tablets (2mg, 3mg, 5mg)

Date of Application: February 29, 2012

Date of Receipt: February 29, 2012

Our Reference Number: NDA 203985

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 29, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application.

Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 2  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Vaishali Jarral, Regulatory Project Manager, at (301) 796-4248.

Sincerely,

*{See appended electronic signature page}*

Vaishali Jarral, M.S., M.B.A  
Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

-----  
**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  
03/08/2012

**Subject:** FW: Application Orientation Presentation- NDA 203985

**Attachments:** Application Orientation.doc

---

**From:** Jarral, Vaishali  
**Sent:** Monday, March 05, 2012 4:35 PM  
**To:** 'Gutman, Nina'  
**Subject:** Application Orientation Presentation- NDA 203985

Hello Ms. Gutman,

This is regarding your request for Application Orientation Presentation for your NDA 203985. The OHOP is granting your request for an "Applicant Orientation Meeting" to provide a slide presentation overview of your NDA submission. These are generally scheduled within 45 days of submission of the BLA/NDA. We are going to hold this meeting on April 6, 2012. I will email you the exact timings in the later emails.

FYI- We do not require a briefing document for this informal meeting, just a slide deck to "guide" the FDA review team through the contents of the NDA submission.

Please see the attached document which contains some advise regarding Application Orientation Presentation and should help you in preparing the presentation.

Please note, that these are general comments and individual applications have unique characteristics. If some comments are inapplicable to the your application and therefore presentation, you should adjust your presentation accordingly.



Application  
Orientation.doc (4...

Thank you,

*Vaishali Jarral, M.S., M.B.A.  
Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products  
CDER/FDA  
301-796-4248*

## **OHOP's General Advice for Application Orientation Presentation Meetings**

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OHOP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

### **Administrative:**

1. Sponsor attendees
2. Presentation outline or Agenda. Should list sections included in submission.

### **Background and Application Specifics:**

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.
4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.
5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.
6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.
7. Regulatory history, including the following:
  - Orphan Drug designation, Fast Track designation
  - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
  - Key Outcomes from FDA Interactions
    - EOP2 Meeting

- Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
- Pre-NDA/BLA meeting
- Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

**Summary Content of NDA/BLA/Efficacy Supplement Sections:**

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

You should also present results of the following, as appropriate:

- Clinical study sites (foreign or domestic)
- Biomarker development for population selection (if applicable)
- Assay validation (if applicable)

120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data
10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
  - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.
11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities
12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics (metabolic pathway, metabolites,  $t_{1/2}$ , ADME, PK in special populations, drug-drug interactions).
13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU)).
14. Risk/benefit profile for drug/biologic
15. Summary
16. Q & A

-----  
**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  
04/09/2012



IND 066279

**MEETING MINUTES**

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

Attention: Yanina Gutman, PharmD  
Associate Director, Drug Regulatory Affairs

Dear Dr. Gutman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RAD001 (everolimus) Tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 27, 2011. The purpose of the meeting was to discuss the proposed filing strategy as well as content and format of a planned NDA for the following indication:



A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

(

If you have any questions, call me at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 27, 2011  
**Meeting Location:** WO22, Room 1311

**Application Number:** IND 066279  
**Product Name:** RAD001 (everolimus)  
**Indication:** SEGA associated with TS, (b) (4)  
**Sponsor/Applicant Name:** Novartis Pharmaceuticals Corporation

**Meeting Chair:** Ke Liu, MD, PhD  
**Meeting Recorder:** Christy Cottrell

### FDA ATTENDEES

Robert Justice, MD, MS, Director, DOP1  
Amna Ibrahim, MD, Deputy Division Director  
Anthony Murgo, MD, MS, FACP, Associate Director, OODP IO  
Ke Liu, MD, PhD, Lead Medical Officer  
Amir Shahlaee, MD, Medical Officer  
Paul G. Kluetz, MD, Medical Officer  
Shenghui Tang, PhD, Team Leader, DB 5  
Somesh Chattopadhyay, PhD, Mathematical Statistician, DB 5  
Qi Liu, PhD, Team Leader, Office of Clinical Pharmacology, DCP5  
Elimika Pfuma, PharmD, PhD, Clinical Pharmacology Reviewer, DCP5  
Christine Garnett, PharmD, Team Leader, Division of Pharmacometrics  
John Duan, PhD, Biopharmaceutics, ONDQA  
Nitin Mehrotra, PhD, Reviewer, Division of Pharmacometrics  
Haripada Sarker, PhD, CMC Lead, ONDQA  
Josephine Jee, PhD, CMC Reviewer, ONDQA  
Shwu-Luan Lee, PhD, Senior Pharmacologist  
Michael Jones, Special Assistant, Office of Regulatory Policy  
Christy Cottrell, Regulatory Project Manager, DOP1

### SPONSOR ATTENDEES

David Lebwohl, MD, Vice President and Global Program Head  
Judith Klimovsky, MD, Executive Director, Global Clinical Program Head  
Gaurav Shah, MD, Global Clinical Leader  
Carlos Garay, MD, Executive Director, US Clinical Development and Medical Affairs  
Pascal Edrich, MSc, Indication Statistician  
Wing Cheung, PhD, Senior Lead Clinical Pharmacokineticist

Jane Xiang, PhD, Global Regulatory Chemistry, Manufacturing and Control  
Joseph Posluszny, PhD, Global Program Regulatory Director  
Daniel Monney, PhD, Global Program Regulatory Manager  
Narin Ahmed, PharmD, Post-doctoral Fellow, Drug Regulatory Affairs  
Yanina Gutman, PharmD, Associate Director, Drug Regulatory Affairs

## BACKGROUND

On October 29, 2010 everolimus received accelerated approval for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection. This approval was based upon a single-arm, single-center study (C2485) and utilized a novel endpoint of volumetric reduction in the size of the primary SEGA lesion. A confirmatory randomized study, M2301, had already begun and was close to completing patient accrual at the time. As volumetric response represented a novel endpoint and clinical benefit in the form of improved overall survival was not clearly demonstrated, two PMRs were issued requiring 4 years of follow up for patients enrolled on both study M2301 and 5 years of follow up for patients enrolled on study C2485.

In addition FDA's review of this sNDA indicated that the potential effect of Afinitor<sup>®</sup> (everolimus) on growth and development of pediatric patients was not adequately assessed as no long-term follow up data is available. Furthermore, non-clinical data indicates that dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females, and increased latency time during the learning and memory phases have been reported in juvenile rat toxicity studies. Cases of low testosterone concentrations associated with high levels of follicle-stimulating hormone have also been reported in the broader clinical everolimus transplant program and no specific evaluation for the presence of hypogonadism has been performed. Based on these findings two post-marketing requirements (PMRs) were issued to the applicant to identify any unexpected serious risk of delayed attainment of developmental landmarks, delayed growth, and hypogonadism in the pediatric population for patients in both trials M2301 and C2845 through long-term follow-up.

In addition to studies in patients with SEGA, the sponsor has also [REDACTED] (b) (4)

[REDACTED]  
Based on [REDACTED] (b) (4)  
findings from study M2301, the applicant is interested in seeking [REDACTED] (b) (4)

[REDACTED]

[REDACTED]  
(b) [REDACTED] (b) (4)  
(c) [REDACTED] (b) (4)

This meeting has been requested to discuss this application further.

**FDA Position:** We recommend that the results of the studies for SEGA (b) (4)  
(b) (4) This position is based upon the following concerns:

(b) (4)

**DISCUSSION**

1. Does the Agency agree to accept the proposed NDA as support for a (b) (4)  
(b) (4)

**FDA RESPONSE:** This will be a review issue.

Although SEGA, (b) (4)  
(b) (4)

**NOVARTIS RESPONSE:** Based on the Agency's recommendation, Novartis will (b) (4)  
(b) (4)  
(b) (4) *Instead, Novartis proposes the following revised submission strategy:*

1. (b) (4)  
(b) (4)  
(b) (4)

(b) (4),

Note: data from SEGA studies (M2301 and C2485) (b) (4)

2. **SEGA submission:** Data from the SEGA (M2301 and C2485) and bioequivalence studies (X2105 and X2106) as well as the CMC information to support the pediatric-appropriate dispersible formulation will be submitted in the context of an NDA to satisfy the requirements outlined in the Written Request (WR) in Q1 2012.

*Per the issued WR, reports from the requested studies (in this case M2301 and C2485) should be submitted with proposed labeling changes that the Sponsor believes are warranted based on the results. Novartis believes that the new information from Study M2301 (a 117-patient, phase-III placebo-controlled trial) and longer-term follow-up from Study C2485 (34.2 months [range: 4.7 to 47.1]) should be communicated within the labeling to allow physicians, patients, and/or caregivers to make a fully informed decision about the benefits and risks associated with everolimus treatment. Furthermore, as patients are likely to require chronic treatment, the longer-term data from Study C2485 are particularly relevant.*

**MEETING DISCUSSION:** FDA will forward the guidance document regarding formatting of Pediatric Exclusivity requests in response to a Written Request. The Agency will accept (b) (4) submissions (b) (4) and NDA for new formulation and SEGA). Filing of these submissions and any changes to the labeling will be a review issue.

2. **Does the Agency agree with the proposed content of the NDA outlined in the draft eCTD table of contents (TOC)?**

**FDA RESPONSE:** Please include an Integrated Summary of Safety (ISS) as part of your final submission. Your proposed TOC appears generally acceptable, but final decision regarding completeness and filability of the application will be made after submission of the full application.

**NOVARTIS RESPONSE:** In light of FDA's feedback, Novartis will submit two dossiers as described in Section 3.1. The Novartis response to the request for an ISS is provided in Section 3.11.

(b) (4)

(b) (4)

[REDACTED] (b) (4)

[REDACTED]

**MEETING DISCUSSION:** [REDACTED] (b) (4)

3. **Novartis believes that data from pivotal Study M2301, longer-term follow up from supportive Study C2485,** [REDACTED] (b) (4)

**FDA RESPONSE:** No. [REDACTED] (b) (4)

**NOVARTIS RESPONSE:** *Novartis acknowledges that the Agency will* [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED] *Novartis wishes to re-emphasize that we remain fully committed to completing the following agreed PMRs:*

- *For Study M2301, providing  $\geq 4$  years of safety and efficacy follow-up from the time of randomization of the last patient (PMR 1700-1) as well as an assessment of the effect of everolimus on growth and development milestones while on treatment (PMR 1700-3)*
- *For Study C2485, providing  $\geq 5$  years of safety and efficacy follow-up from the start of treatment for the last patient (PMR 1700-2) as well as an assessment of the effect of everolimus on growth and development milestones while on treatment (PMR 1700-4)*

**MEETING DISCUSSION:** None.

4. **Novartis believes that this application is exempt from a User Fee as everolimus has been assigned orphan drug designation for the treatment of TSC. Does the Agency agree that a User-fee Waiver is acceptable?**

**FDA RESPONSE:** Under section 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act, a human drug application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the Act is not

subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition. Even though your new indication may be orphan designated, we believe [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED] For further information, please contact Michael Jones in CDER's Office of Regulatory Policy (phone 301-796-3602).

**NOVARTIS RESPONSE:** *Novartis believes that [REDACTED] (b) (4), TSC-associated SEGA) are covered by the following orphan designation issued for everolimus on 08-Jun-2009 (designation request # 09-2836): 'Treatment of patients with TSC including TSC-associated SEGA, [REDACTED] (b) (4), [REDACTED]'*

*Novartis would like to seek clarification from the Agency regarding the feedback that we will not meet the user-fee exemption because [REDACTED] (b) (4)*

**MEETING DISCUSSION:** **If your new drug application includes only orphan designated indications, an application fee would not be required. Separate labeling for the dispersible formulation would be acceptable. Any new tradename associated with the new formulation would require a review by OSE.**

5. **Novartis proposes to cross-reference the Afinitor NDA (22-334) for all everolimus drug substance and non-clinical information as well as select clinical pharmacology information. Does the Agency agree with this approach?**

**FDA RESPONSE:** This appears acceptable. You may cross reference information for the everolimus drug substance approved in NDA 22-334 provided that the following CMC information is submitted to the new NDA.

- Acceptable LOA, with information location
- Complete manufacturing site information
- Nomenclature
- Description
- Molecular Structure
- Molecular Weight
- Molecular Formula
- Physicochemical Properties
- Specifications
- Stability Protocol and Stability Commitment
- Stability Data

A final determination of acceptability will be made during the NDA review.

**NOVARTIS RESPONSE:** *Novartis acknowledges FDA's response. In place of re-submitting the requested information, Novartis proposes to provide a tabular listing of the current modules in NDA 22-334 indicating where this information is located.*

**MEETING DISCUSSION:** FDA requests that the basic information listed above be resubmitted with this proposed new NDA and all future updates be submitted to both NDAs.

6. To satisfy the agreement for an age-appropriate/pediatric formulation described in the WR, Novartis plans to seek marketing authorization for the 2-mg, 3-mg, and 5-mg dispersible tablets. Does the Agency agree?

**FDA RESPONSE:** Although the proposed dispersible tablets appear to be age-appropriate pediatric formulations, the final determination regarding satisfaction of the terms of the WR is made by the Pediatric Exclusivity Board.

**MEETING DISCUSSION:** None.

7. Novartis proposes to include (b) (4) in the NDA submission. It will be (b) (4) all strengths. All batch records will be available at the site of manufacture for the pre-approval inspection. Does the Agency agree with this approach?

**FDA RESPONSE:** We do not have information on the 2 mg and 3 mg tablets; therefore, you may need to provide complete CMC information for these two strengths. You may cross reference information on your approved 5 mg tablet; however, a final determination of acceptability for all proposed specifications, batch analysis and stability data will be made at the time of NDA review. You should propose to include (b) (4) executed batch records in your NDA submission.

**NOVARTIS RESPONSE:** *Novartis wishes to clarify that complete CMC information will be provided for the 2-mg, 3-mg, and 5-mg dispersible tablets in the NDA submission.*

*In addition, we would like to clarify why we proposed to submit (b) (4) (b) (4). Three batches would require submission of (b) (4) information since the 2-mg, 3-mg, and 5-mg dispersible tablets (b) (4) are manufactured by the same manufacturer. Furthermore, the submission of (b) (4) was deemed acceptable in the original Afinitor NDA.*

**MEETING DISCUSSION:** The FDA requires submission of (b) (4) executed bulk batches and (b) (4) validation (b) (4).

**POST-MEETING NOTE:** Following the meeting, both the sponsor and FDA agreed to revise the Meeting Discussion above as follows to more accurately reflect the mutual

**understanding:**

Since (b) (4) is used to manufacture the 2-mg, 3-mg, and 5-mg dispersible tablets, the Sponsor will submit (b) (4) dispersion and (b) (4) batch record reflecting the tableting process for each strength.

8. Novartis intends to submit (b) (4). Does the Agency agree with this approach?

**FDA RESPONSE:** As per the Agency's 21<sup>st</sup> Century initiative, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a commercially viable shelf life. Amendments submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

**MEETING DISCUSSION:** None.

9. Does the Agency agree that the biopharmaceutical plan as outlined below is adequate to support the approval of the new formulation of Afinitor dispersible tablets?

**FDA RESPONSE:** Yes, we tentatively agree from the Biopharmaceutics perspective. Please provide the following information for clarification and further discussion.

1. Is the 1-mg tablet the only strength used in Study M2301?
2. (b) (4)
3. What are the differences among the formulations used in studies M2301 (b) (4) and C2485 beside the strength differences?

**NOVARTIS RESPONSE:** The following tablet strengths were used in the (b) (4) studies:

- Study M2301: 1 mg (b) (4)
- Study C2485: 2.5 mg and 5 mg

The 1-mg everolimus tablet and the higher strengths of the everolimus tablets (2.5 mg and 5 mg) are (b) (4) the drug substance and amounts of the excipients. The 2.5-mg and 5-mg tablets are manufactured with a (b) (4) solid dispersion, whereas the 1-mg strength tablet is manufactured with a (b) (4) solid dispersion.

**MEETING DISCUSSION:** None.

**10. Does the Agency agree that the study populations and endpoints assessed across these trials are appropriate to support the proposed indication?**

**FDA RESPONSE:** No. See Question 1. Any change in current SEGA indication will require the long-term follow up data required as part of the PMRs issued at the time of accelerated approval.

(b) (4)

Finally, responses to everolimus therapy in skin lesions and facial angiofibromas represent a secondary endpoint in studies M2301 (b) (4) and as such will need to be evaluated in the context of the primary efficacy endpoint results.

***NOVARTIS RESPONSE:** Novartis acknowledges that the Agency will not consider conversion to regular approval for the SEGA indication at this time. However, Novartis will submit new information that should merit a label update in accordance with the intent of the issued WR and may support minimal modifications to the indication to better guide decision making by physicians, patients, and/or caregivers with regard to Afinitor.*

**MEETING DISCUSSION: None.**

**11. Does the Agency agree to the**

(b) (4)

(b) (4)

**MEETING DISCUSSION: The FDA agrees with the sponsor's proposal for a waiver of**

(b) (4)  
(b) (4) **FDA requests that updated safety information on the Zortress pediatric transplant population be submitted, if available.**

12. **Does the Agency agree to the Novartis proposal to provide** (b) (4)

(b) (4)

**FDA RESPONSE:** No. Please see answer to question #2 and #11. We agree with your proposal to not submit an ISE.

**NOVARTIS RESPONSE:** *See Novartis response to Question 11 (Section 3.11)*

**MEETING DISCUSSION: None.**

13. **Does the Agency agree with our proposal for patient narratives and case report forms (CRFs) to be provided in support of this application?**

**FDA RESPONSE:** Yes. However, CRFs for additional patients may need to be submitted for review and should be available with 48 hour notice.

**MEETING DISCUSSION: None.**

14. **Does the Agency agree with the proposed content for the Safety and Efficacy Update?**

**FDA RESPONSE:** Yes, however, any additional efficacy data submitted at the time of a 90-day update may be considered a major amendment and trigger extension of the review clock.

**NOVARTIS RESPONSE:** *Based on the revised submission strategy (Section 3.1) as well as the feedback provided in FDA's response above, Novartis wishes to propose the following strategy for the Safety Update (Note: an Efficacy Update will not be provided).*

(b) (4)

### **SEGA Safety Update**

*Novartis proposes to provide a Safety Update for Study M2301 within 3 months of the original submission to support a potential priority review. This update will provide approximately 4 months of additional safety data via an addendum to the SCS (Module 2.7.4).*

- *The SCS addendum will include tables with core, blinded phase data from the cut-off date included in the original submission (02-Mar-2011) presented side-by-side with blinded phase data from the new cut-off date which corresponds to the date that the last placebo patient from the core phase of Study M2301 begins treatment in the extension phase or discontinues from the study (18-Jul-2011). All data collected in the trial while on everolimus therapy (including in the double-blind phase, extension phase, or after cross-over from placebo) will be presented in separate tables.*
- *Patient narratives and CRFs will be provided for cases of death, SAEs (irrespective of relationship to study drug), discontinuations due to AEs, and cases of amenorrhea; these will be included in Modules 5.3.5.3 and 5.3.5.1, respectively.*
- *Updated CRTs for safety, PK, and biomarker parameters from Study M2301 will be provided in Module 5.3.5.1.*
- *Novartis will provide an updated proposed label reflecting the additional information from Study M2301 included in the Update.*

*Note: additional data from Study C2485 will not be provided with the Update. The original NDA submission will include an updated CSR for Study C2485 corresponding to an additional 9 months of safety, efficacy and PK data (up to a 31-Dec-2010 cut-off date).*

**MEETING DISCUSSION: The cut-off dates for Novartis' submission of safety data**

(b) (4)

(b) (4)

**The cut-off dates for the**

**SEGA trial was 3/2/11 (original) and 7/18/11 (follow-up); with an anticipated submission date of 1Q2012. The FDA agrees with these proposed dates.**

15. **Novartis plans to submit the raw and derived datasets for efficacy and safety endpoints of Studies M2301 (b)(4) and C2485, as well as raw and derived datasets for PK parameters of Studies X2105 and X2106. Statistical Applications Software (SAS) analysis programs for the primary and key secondary analyses of Studies M2301 and (b)(4) will also be provided. Does the Agency agree?**

**FDA RESPONSE:** Yes.

**MEETING DISCUSSION:** None.

**ISSUES REQUIRING FURTHER DISCUSSION**

None.

**ACTION ITEMS**

| Action Item/Description                                                                              | Owner | Due Date |
|------------------------------------------------------------------------------------------------------|-------|----------|
| FDA to send guidance document regarding format of Pediatric Exclusivity submission in response to WR | FDA   | ASAP     |

**ATTACHMENTS AND HANDOUTS**

None.

\_\_\_\_\_  
Christy Cottrell  
Regulatory Project Manager  
Minutes Recorder

Concurrence: \_\_\_\_\_  
Ke Liu, MD, PhD  
Clinical Team Leader  
Meeting Chair

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

/s/  
-----

CHRISTY L COTTRELL  
10/11/2011

KE LIU  
10/11/2011



**DEPARTMENT OF HEALTH AND HUMAN  
SERVICES**

---

**Food and Drug  
Administration Silver  
Spring MD 20993**

IND 66,279

**MEETING MINUTES**

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

Attention: Yanina Gutman, PharmD, RAC  
Senior Regulatory Manager, Drug Regulatory Affairs

Dear Dr. Gutman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Everolimus (RAD001).

We also refer to the meeting between representatives of your firm and the FDA on September 29, 2009. The purpose of the meeting was to discuss the filing strategy, content and format of a planned supplemental NDA for subependymal giant cell astrocytoma.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Christy Cottrell  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Enclosure



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND  
RESEARCH**

---

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-sNDA

**Meeting Date and Time:** September 29, 2009 at 2:30 pm  
**Meeting Location:** WO22, Room 1309

**Application Number:** IND 66,279  
**Product Name:** Everolimus (RAD001)  
**Indication:** Subependymal giant cell astrocytoma  
**Sponsor/Applicant Name:** Novartis

**Meeting Chair:** V. Ellen Maher, MD  
**Meeting Recorder:** Christy Cottrell

**FDA ATTENDEES**

Robert Justice, MD, Director, DDOP  
Tony Murgo, MD, Deputy Director, OODP  
V. Ellen Maher, MD, Clinical Team Leader  
Qin Ryan, MD, Clinical Reviewer  
Shenghui Tang, PhD, Biometrics Team Leader  
Somesh Chattopadhyay, PhD, Biometrics Reviewer  
Jeff Fritsch, Director, Regulatory Affairs, Office of Orphan Products  
Christy Cottrell, Regulatory Project Manager

**SPONSOR ATTENDEES**

(b) (4)

Nina Gutman, PharmD, RAC, Senior Regulatory Manager  
Joseph Posluszny, PhD, Global Program Regulatory Director  
Lynne McGrath, MPH, PhD, North American Head of Drug Regulatory Affairs  
David Lebwohl, MD, VP and Global Program Head, Afinitor  
Tarek Sahmoud, MD, PhD, Global Clinical Program Head  
Matthew Robson, MD, MRCP, Senior Global Clinical Leader  
Betty Molloy, MSc, Expert Biostatistician  
Jaqueline Rogerio, MD, Medical Director, US Clinical Development & Medical Affairs  
Peter Berry, Senior Director, Clinical Submissions  
Soraya Madani, Rockville Office

## BACKGROUND

Study C2485 “Everolimus (RAD001) Therapy of Giant Cell Astrocytoma in Patients with Tuberous Sclerosis Complex” is, a 28-patient investigator-initiated, Phase 2 study currently being conducted under IND No. 70,895. A preliminary analysis of results from this study showed promising efficacy with acceptable toxicity. Based on these results, Novartis has restructured their filing strategy and intends to use the data obtained from the ongoing Phase 3 pivotal study, M2301, to confirm the clinical benefit and safety of everolimus in patients with TSC-associated SEGA demonstrated in Study C2485.

Draft responses were sent to the sponsor on September 23, 2009.

## DISCUSSION

1. Novartis is planning to seek approval of everolimus for the treatment of patients with SEGA associated with TSC on the basis of data from Study C2485 under 21 CFR 314 Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. **Does the Agency agree that data from** (b) (4)

**FDA RESPONSE:** No. (b) (4)

We recommend you complete the randomized Phase III trial before submitting the application for marketing approval.

**NOVARTIS RESPONSE:** We acknowledge the Division’s answer and would like to clarify that until recently we shared the same position and have committed to conducting a phase III randomized, placebo controlled study further investigating everolimus for the treatment of patients with TSC-associated SEGA.

Professor David Franz, MD, the Principal Investigator of Study C2485 brought his results to our attention and explained the importance of these data and the unmet medical need for a population that is

- lacking an approved pharmacological treatment option
- faced with the morbidities of the disease or a complicated surgical intervention

After careful consideration of the quality of the data and the available options for these patients, Novartis decided that these data warranted being brought to the attention of the Division.

Novartis would welcome the opportunity of working with the Agency, the medical community, and patient advocacy groups to facilitate the filing and review of an application based on these data and to that end would like to seek further clarification from the Division on your response with the following objectives:

- to gain insight and reach agreement on the level of evidence required for filing for Accelerated Approval under Subpart H for patients with TSC-associated, progressing, SEGAs in terms of the
  - magnitude and robustness of the efficacy and measures of clinical benefit required
  - extent of the safety data
  - rarity of the patient population and lack of available treatment options
- to obtain advice from the Agency on how to optimize this data package; potential examples might include
  - extended safety and efficacy follow-up
  - additional statistical analyses
  - providing the Division with all available scans for review

**MEETING DISCUSSION:** *The sponsor made a strong case for the submission of (b) (4) for Subpart H approval. FDA agrees to review the data. FDA also requested that additional safety information be submitted with the application. FDA recommends that all patients be followed for at least one year and that safety and efficacy data be provided at the time of submission. The sponsor intends to complete recruitment to their Phase 3 trial prior to the action date for the supplemental application. Sponsor will submit a 3-month update for both efficacy and safety after supplement is submitted.*

2. Study M2301 is a phase-III randomized, double-blind, placebo-controlled study of everolimus in patients with TSC-associated SEGA that is designed to further verify and describe the clinical benefit of everolimus in a patient population similar to that in Study C2485. **Does the Agency agree that (b) (4) everolimus in this indication?**

**FDA RESPONSE:** No. See response to Question 1. Whether the results of your proposed randomized study would be able to demonstrate clinical benefit is a review issue.

**Post-Meeting Comment:** *See meeting discussion under Question 1.*

3. (b) (4)  
regulatory purposes?

**FDA RESPONSE:** No. See response to Questions 1 and 2.

Based on your M2301 protocol submitted in this meeting package, patients of any age (n =99) would be eligible. This is inconsistent with your PPSR submission, which stated patients age “birth to 18” (n = 99) will be enrolled in a randomized (2:1) SEGA/STC study. Please clarify this discrepancy.

In addition, whether study M2301 will be sufficient for a Written Request is currently under review.

**NOVARTIS RESPONSE:** The Division is correct in that protocol M2301 submitted as part of the pre-sNDA briefing package indicates that patients of any age diagnosed with TSC-associated SEGA are eligible for entry into the study. In the PPSR, Novartis has indicated that while the anticipated total sample size is 99 patients, based on the epidemiology of the disease, at least 74 evaluable patients from birth to less than 18 years will be enrolled.

*Post-Meeting Comment: FDA must issue a Written Request before the supplement is submitted if you wish to receive Pediatric Exclusivity.*

4. Novartis proposes the following primary efficacy endpoint for Study C2485:

(b) (4)  
Does the Agency agree with this proposal?

**FDA RESPONSE:** No. See response to Questions 1 and 2.

*Post-Meeting Comment: We agree with your plan to assess the primary endpoint at 6 months. Sponsor agreed that all patients from C2485 would have minimum of 12 months follow-up for efficacy.*

*In your submission, please provide:*

- *An overview of the evolution of this study’s primary endpoints;*
- *Your rationale for your primary endpoint-assessment of the change in tumor volume at 6 months; and*
- *An assessment of drug activity using each of these endpoints.*

5. (b) (4)

[REDACTED] (b) (4)

**FDA RESPONSE:** No. See response to Questions 1 and 2.

**MEETING DISCUSSION:** See Question 1. Per Q1 discussion, FDA agrees with the sponsor's proposal. Division would like to see your data from the pediatric transplant studies and TSC studies other than SEGA. Division asked sponsor to submit list of items to be included in Sections 2.7.2, 2.7.3 and 2.7.4.

**Post-Meeting Comment:** We agree that an ISE and ISS are not necessary. We agree with your plan to provide side by side tables for studies C2485 and B351. Please state your plans to include safety data from Study M2301 in the 120 day safety update.

6. [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Does the Agency agree to the approach outlined above for the Safety Update?

**FDA RESPONSE:** No. See response to Questions 1 and 2.

**Post-Meeting Comment:** See meeting discussion for Question 1. Our understanding is that your efficacy data will use a cut-off of December 2009 (to provide 12 months of efficacy data). Please provide a cut-off of November 2009 for the safety data submitted in your initial supplemental NDA.

7. [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Does the Agency agree to [REDACTED] (b) (4) described above?

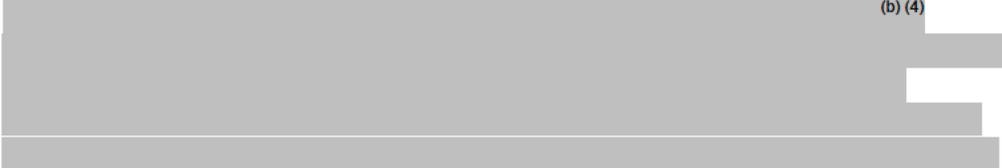
**FDA RESPONSE:** See response to Questions 1 and 2.

*Post-Meeting Comment: Yes.*

8. Currently, Afinitor (everolimus) is commercially available as 5-mg and 10-mg tablets. In Study C2485, 2.5-mg and 5-mg tablets are being utilized to maintain everolimus whole blood concentrations within a 5-15 ng/mL range. In Dec-2009, Novartis will submit a prior approval supplement for 2.5-mg tablets. **Based on the available tablet strengths, the initial dosing and adjustment guidelines used in Study C2485, as well as the clinically meaningful results observed and acceptable safety profile, does the Agency agree that 2.5-mg and 5-mg tablets are appropriate with regard to formulation and strength for dosing patients with SEGA associated with TSC?**

**FDA RESPONSE:** The 2.5-mg and 5-mg tablets are appropriate for study C2485. However, ongoing and future studies should use the 1-mg tablet formulation or the proposed pediatric formulation, if available, in patients with SEGA associated with TSC. The results of the 1-mg tablet formulation may need to be bridged with your proposed pediatric formulation.

**NOVARTIS RESPONSE:** Novartis agrees.

9. (b) (4)  
  
**Does the Agency agree that this approach for data acquisition can meet FDA expectations for filing an sNDA?**

**FDA RESPONSE:** No. See response to Questions 1 and 2.

*Post-Meeting Comment: This is a review issue.*

*Regarding your proposed eCRF, please include the following:*

- a. Genetic test, if any, under TSC diagnosis, pages 3-4;
- b. Sum of the subject's major and minor features under TSC diagnosis, pages 3-4;
- c. Measurable criteria for  (b) (4) documentation on page 31;
- d. Please place page 42 (Prior anti-TSC therapy) after page 7 (Relevant medical history); and
- e. Information on the extent of missing follow-up information and the reason this information is missing (on page 44).

10. (a) [REDACTED] (b) (4)

**Does the Agency agree with this primary efficacy analysis?**

**FDA RESPONSE:** See response to Questions 1 and 2. The assumption of [REDACTED] (b) (4) may not be valid. Please use a nonparametric method.

**NOVARTIS RESPONSE:** Novartis agrees. Based on the central limit theorem and the observed distribution of the data (as per local investigator assessment), the primary variable is expected to be robust for the assumption of normality. However, the statistical analysis plan will be modified so that the assumption of normality will be assessed and if found not to hold, a non-parametric Wilcoxon test will be applied. If the normality assumption is valid, then the result of the Wilcoxon test will be presented as a supportive analysis.

**MEETING DISCUSSION:** *Division agrees.*

(b) In addition to the [REDACTED] (b) (4)

**Does the Agency agree that the proposed analysis methods are adequate to support filing of everolimus, in particular the aspects of the analyses highlighted above?**

**FDA RESPONSE:** No. See response to Questions 1 and 2.

**Post-Meeting Comment:** *See response to Question 4.*

11. Novartis plans to submit the following datasets and programs for the review of efficacy, pharmacokinetics, and safety of everolimus in patients with TSC-associated SEGAs:

- [REDACTED] (b) (4)

**Does the Agency agree with this proposal?**

**FDA RESPONSE:** No. See response to Questions 1 and 2.

**Post-Meeting Comment:** *Per discussion in Question #1, the proposed datasets are acceptable. In addition, please submit safety datasets of other pediatric studies, if they are available. Please also see response to Question 5.*

**Post-Meeting Questions and Responses:**

Below are the Division's responses to the follow-up questions posed in the submission dated November 6, 2009.

1. Does the Agency agree with the proposed table shells for side-by-side comparison of data from Studies C2485 and B351 to appear in Section 2.7.4 (see [Appendix 2])?

**FDA RESPONSE:** Yes.

2. Does the Agency agree with our proposal not to submit the CSRs and datasets from Studies B351, B257, and B258?

**FDA RESPONSE:** Yes.

3. Does the Agency agree with our proposal to provide (b) (4)

**FDA RESPONSE:** No. Please provide blinded tabular summaries of the SAEs.

4. Does the Agency agree to granting waivers for Sections 2.7.2 and 2.7.3 as Novartis plans to include all relevant information in the Study C2485 CSR?

**FDA RESPONSE:** Yes.

5. Does the Agency agree with the proposed content of the sNDA submission as outlined in the revised eCTD table of contents (see [Appendix 3])?

**FDA RESPONSE:** Yes.

**ISSUES REQUIRING FURTHER DISCUSSION**

None

**ACTION ITEMS**

None

**ATTACHMENTS AND HANDOUTS**

None

Concurrence:

\_\_\_\_\_  
Christy Cottrell  
Regulatory Project Manager  
Meeting Recorder

\_\_\_\_\_  
V. Ellen Maher, MD  
Clinical Team Leader  
Meeting Chair

| Application Type/Number | Submission Type/Number | Submitter Name                       | Product Name |
|-------------------------|------------------------|--------------------------------------|--------------|
| IND-66279               | GI-1                   | NOVARTIS<br>PHARMACEUTICA<br>LS CORP | RAD001       |

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

/s/

-----  
CHRISTY L COTTRELL  
12/03/2009

VIRGINIA E MAHER  
12/04/2009

**TELECON MEETING MINUTES**

**MEETING DATE:** September 18, 2008    **TIME:** 12:00    **LOCATION:** 2376 WO

**IND:** 66,279            **Meeting Request Receipt Date:** July 15, 2008

**FDA Response Date:** July 28, 2008            **Briefing Document Receipt Date:** July 15, 2008

**DRUG:** RAD001 (everolimus) Tablets            **INDICATION:** Tuberous Sclerosis Complex

**SPONSOR:** Novartis Oncology            **TYPE of MEETING:** Clinical SPA Type A

**FDA PARTICIPANTS AND TITLES:**

Ramzi Dagher, M.D., Deputy Director, CDER/OND)/OODP/Division of Drug  
Oncology Products (DDOP)

Amna Ibrahim, M.D., Clinical Team Leader, CDER/OND/OODP/DDOP

Qin Ryan, M.D., Medical Officer, CDER/OND/OODP/DDOP

Rajeshwari Sridhara, Ph.D., Biometrics Team Leader, DBV/OB/CDER

Qi Liu, Ph.D., Acting Clinical Pharmacology Team Leader and Reviewer, OCP/CDER

Brenda Atkins (for Susan Jenney), Regulatory Project Manager,  
CDER/OND/OODP/DDOP

**INDUSTRY PARTICIPANTS AND TITLES:**

Sibylle Jennings, PhD, Associate Director, DRA Oncology Global Development (US)

Patricia van den Broeck, MSc, Global Program Regulatory Director RAD001, Oncology  
Global Development

Daniel Monney, DRA Manager, DRA Oncology Global Development (Basel)

Lynne Fahey McGrath, MPH, PhD, U.S. Head DRA, Oncology Global Development  
(unconfirmed)

Tarek Sahmoud, MD, PhD, Executive Medical Director, Oncology Global Development

James Ford, MS, Senior Clinical Manager, Oncology Global Development

Li Li, PhD, DABT, Senior Fellow Preclinical Safety

Emmanuel Zuber, PhD, Unit Head I, Oncology Biostatistics

**BACKGROUND:**

The sponsor submitted a Special Protocol Assessment (SPA) request (b) (4)

[REDACTED]

[REDACTED]

(b) (4)  
[Redacted text block]

(b) (4)

[Redacted text block containing multiple paragraphs of obscured content]

**ACTION ITEMS:** Discussion items should be taken into consideration for future actions.

see electronic signature page  
Brenda Atkins for Susan Jenney  
Regulatory Project Manager  
(signed paper version 10-15-08)

Concurrence Chair: see electronic signature page  
Amna Ibrahim, M.D.  
Clinical Team Leader, DODP  
(concurred on paper version 10-16-08)

Linked Applications

Sponsor Name

Drug Name

-----  
IND 66279

-----  
NOVARTIS  
PHARMACEUTICALS  
CORP

-----  
RAD001

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

/s/

-----  
AMNA IBRAHIM  
10/17/2008

# MEETING MINUTES

**MEETING DATE:** October 2, 2007    **TIME:** 2:00    **LOCATION:** 1421

**IND:** 66,279    **Meeting Request Receipt Date:** June 1, 2007  
**FDA Response Date:** July 11, 2007  
**Briefing Document Receipt Date:** July 17, 2007

**DRUG:** RAD001 (everolimus)    **INDICATION:** tuberous sclerosis complex

**SPONSOR:** Novartis    **TYPE of MEETING:** EOP2

**FDA PARTICIPANTS:** Robert Justice, M.D., Dir., DDOP  
Ramzi Dagher, M.D., Dep. Dir., DDOP (pre-meeting)  
Amna Ibrahim, M.D., Medical Team Leader, DDOP (Chair)  
Qin Ryan, M.D., Medical Officer, DDOP  
Ramesh Raman, M.D., Medical Officer, DNDP  
Eric Bastings, M.D., Medical Team Leader, DNDP  
Melanie Blank, M.D., Medical Officer, DCRDP (pre-meeting)  
Brigitte Widemann, M.D., Visiting Scientist, NIH (pre-meeting)  
Sophia Abraham, Ph.D., Clin. Pharm. Reviewer, OCP (pre-mtg)  
Shenghui Tang, Ph.D., Statistician, OB  
Tamy Kim, Project Manager, DNDP  
Dotti Pease, Project Manager, DDOP

## **SPONSOR:**

### **Novartis Participants**

Arlene Wolny, Ph.D. (Director, Drug Regulatory Affairs, Oncology)  
Myra R Herrle, Ph.D. (Senior Associate Director, Drug Regulatory Affairs US, Oncology)  
Tarek Sahmoud, M.D. (Executive Director, Oncology Clinical Research)  
Emmanuel Zuber, Ph.D. (Unit Head, Oncology Biostatistics & Statistical Reporting)  
Wendy Hayes, D.O. (Director Clinical Imaging)  
Wing K Cheng, Ph.D. (Sr. Lead Clinical Pharmacokineticist, Clinical Pharmacology, Oncology)  
Shalini Jain, Assoc. Dir., Drug Regulatory Affairs, Novartis

### **External Clinical Consultant**

(b) (4)

**MEETING OBJECTIVES:** Discuss proposed trials for TSC and sponsor's questions

**BACKGROUND:** Novartis proposes to conduct the following two studies in TSC:

- A randomized, double-blind, placebo-controlled study in the treatment of angiomyolipomata (AML) in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis
- A randomized, double-blind, placebo-controlled study in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex

Novartis presented the attached slides at the meeting in response to FDA's responses to their questions.

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

AML (angiomyolipomata)

1. We plan to conduct one pivotal phase III placebo-controlled study with 99 patients with AML. Novartis considers [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] Does the Agency agree?

**FDA –** [REDACTED] (b) (4)  
[REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

2. Novartis believes that the [REDACTED] (b) (4)

[REDACTED]  
[REDACTED] Does the Agency agree?

**FDA – No.** [REDACTED] (b) (4)

[REDACTED] (b) (4)  
[REDACTED]

3. The primary morbidity in patients with AML results from increases in tumor volume. To document efficacy of RAD001, [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)  
 [REDACTED]  
 [REDACTED]  
 [REDACTED]. Does the Agency agree?

**FDA –No. See response to questions 1 and 2. If you plan to use an approach that**  
 [REDACTED] (b) (4)  
 [REDACTED]  
 [REDACTED]

- 4. The calculation of response rate will be based only on AML lesions in this protocol. If the patient had other conditions that are TSC-related, e.g., SEGAs, seizures, LAM, skin lesions, etc., changes in these lesions and conditions will be reported separately but will not be included in the calculation of response rate. Does the Agency agree?

**FDA – It is not clear how lesions that are not from AML would be handled if they demonstrate progression. The Independent Review Charter should be provided at the time of the SPA.**

- 5. We believe that the specific safety monitoring described in the protocol outline is adequate to document the safety of RAD001 in this target patient population. Does the Agency agree?

**FDA – No. Patients with a benign disease may be treated with RAD001 for a longer duration than cancer patients. These patients may be at greater risk from long term treatment with RAD001. Monitoring for pneumonitis should be performed at baseline and continued at prespecified intervals through out treatment for all patients.**

**We recommend longer follow-up for toxicity after discontinuation because we have concerns regarding long term treatment and toxicity.**

SEGA

- 6. We plan to conduct [REDACTED] (b) (4)  
 [REDACTED]  
 [REDACTED] to support approval in the following indication: *Treatment for patients with subependymal giant cell astrocytomas associated with tuberous sclerosis complex.* Does the Agency agree?

**FDA - No. Details of how the diagnosis of SEGA will be made should be provided. Patients with tuberous sclerosis may have other benign tumors involving the brain. Considering that it may be difficult to differentiate between the TS associated tumors, summing up all the lesion volumes by MRI may not reflect an effect only on**

**SEGA. In addition, measuring brain tumors accurately and reliably and in a standardized way in various international sites may be problematic.**

**For these reasons, [REDACTED] (b) (4) alone would not be sufficient to support approval. Demonstration of clinical benefit would be required. Percentage of patients who develop hydrocephalus could be a primary endpoint.**

7. Novartis believes that the patient population to be studied, as defined in the inclusion and exclusion criteria of protocol CRAD001M2301, represents a population with a clear unmet medical need. Does the Agency agree?

**FDA – This patient population qualifies as an unmet medical need. However, you must define criteria for diagnosis of SEGA lesions and include factors that can reliably differentiate them from other brain tumors in patients with TS. See answer to question 6.**

8. The proposed CRAD001M2301 (SEGA) protocol allows inclusion of patients of age three years and above. Patients will be dosed at starting dose of 4.5 mg/m<sup>2</sup>/day. Does the Agency agree with the choice of the age group and that the planned dosing regimen and schedule of safety assessment are adequate for this age group?

**FDA – We agree with the choice of age group.**

**We are concerned that the need for dose adjustment may break the blinding to both the patient and the investigator.**

**We have concerns regarding long term treatment and toxicity. See response to question #5.**

9. The primary morbidity in patients with SEGA results from increases in tumor volume. To document efficacy of RAD001, [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED] Does the Agency agree?

**FDA - See response to question 6.**

10. The calculation of response rate will be based [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED] Does the Agency agree?

**FDA – See response to question 4 and 6.**

11. Children enrolled in the CRAD001M2301 study will have a neuropsychological evaluation (baseline, 12, 24 weeks post-treatment) using standardized age-appropriate tests, including:

- [REDACTED] (b) (4)

Does the Agency agree these are adequate tools to assess any potential changes in intelligence, motion, behavior, and/or language following treatment with RAD001 in this randomized, placebo controlled study of patients with SEGA?

**FDA – These tools are not sufficient to comprehensively measure neuropsychiatric changes. They may be useful as secondary endpoints which are considered exploratory. The neuropsychiatric changes may or may not be related to SEGA tumors.**

12. We believe that the [REDACTED] (b) (4) in this target patient population. Does the Agency agree?

**FDA – We recommend longer follow-up for toxicity after discontinuation because we have concerns regarding long term treatment and toxicity.**

**ADDITIONAL FDA COMMENTS**

**FDA – we strongly recommend submitting SPAs for these trials, including SAPs, sample CRFs, and IRCs. Novartis agreed to let us know beforehand when/if they will be submitted so that we can arrange consultant(s).**

**QT Evaluation**

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

**Additional Clinical Pharmacology Comments:**

1. According to 21CFR 320.25, you should assess the bioavailability of RAD001 (absolute or relative) from the proposed for marketing tablet formulation

2. We recommend that you explore the relationships between trough plasma RAD001 levels and both overall response rate and major toxicity in your proposed Phase 3 Studies CRAD001M2301 and CRAD001M2302.

**ACTION ITEMS:**

Novartis will notify FDA beforehand if they intend to submit SPAs for these studies.

\_\_\_\_\_  
Dotti Pease  
Chief, Project Management Staff

**Concurrence Chair:** \_\_\_\_\_  
Amna Ibrahim, M.D.  
Medical Team Leader

ATTACHMENT: Novartis slides

32 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

-----  
Amna Ibrahim

10/18/2007 08:39:33 AM