CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-334 SUPPL # HFD # 150

Trade Name Afinitor tablets

Generic Name everolimus

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known March 30, 2009

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.

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?

5 years

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?

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#

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:

(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: Christy Cottrell
Title: Consumer Safety Officer
Date: 4-1-09

Name of Office/Division Director signing form: Robert Justice, MD
Title: Division Director, DDOP

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/

Christy Cottrell
4/1/2009 02:00:45 PM

Robert Justice
4/1/2009 06:35:17 PM

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

NDA/BLA#: NDA 22-334 Supplement Number: n/a NDA Supplement Type (e.g. SE5): n/a

Division Name: DDOP PDUFA Goal Date: 3-30-09 Stamp Date: 6/30/2008

Proprietary Name: Afinitor

Established/Generic Name: everolimus

Dosage Form: Tablets

Applicant/Sponsor: Novartis

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): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Advanced renal cell carcinoma

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∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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 for mulation. 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) 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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	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?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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

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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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 DAR RTS 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.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: 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∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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.

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.*)

∆ 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 for mulation. 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 Section 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 Secti on E); and/or (4) additional studies in other age groups that are not needed because efficacy i s being extrapolated (if so, proceed to Section F).. Note that mor e than one of these options may apply for this i ndication to cover all of the pediatric subpopul ations.

Section C: Deferred Studies (for some or all 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 Approva l in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

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

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

* Other Reason: _____

† Note: Studies may only be deferre d 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 w ill be conducted with due diligence and at the ea rliest possible time, and a timeline for the completion of the studies. If studies are deferre d, 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 w ill 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 specifi es a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covere d through partial w aivers and deferrals, P ediatric Page is complete and should be signed. If not, compl ete the rest of the P ediatric Page as appli cable.

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?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

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
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	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 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?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	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.

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

Christy Cottrell
3/20/2009 03:34:35 PM
PeRC meeting held on 2/11/09: Waiver

Afinitor® (everolimus) tablets
NDA22-334

(Advanced Renal Cell Carcinoma Indication)

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.

Lynne F. McGrath, MPH, Ph.D
Executive Director
Drug Regulatory Affairs

Date 6/12/2008

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 22-334 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Afinitor Established/Proper Name: everolimus Dosage Form: Tablets		Applicant: Novartis Pharmaceuticals Agent for Applicant (if applicable):
RPM: Christy Cottrell		Division: DDOP

NDAs: NDA Application Type: X 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	March 30, 2009 March 30, 2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____	☐ Received

[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.

❖ Application[2] Characteristics	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): 1 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	2/11/09
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Burst email, Information Alert

[2] All questions in all sections pertain 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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? (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))).	☐ Yes ☐ No
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? (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))).	☐ Yes ☐ No
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*).* *If "No," continue with question (5).*	

(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? (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). *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). *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	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 *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval letter dated 3-30-09
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Included; 3-30-09
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	12-22-08 revised PPI
• Original applicant-proposed labeling	6-27-08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	See FPI
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	12-22-08
• Original applicant-proposed labeling	6-27-08
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	2-23-09
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEDP ☒ DRISK 11-6-08 ☒ DDMAC Attended labeling mtgs ☐ CSS ☒ Other reviews SEALD 3/20/09
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	8-21-08; 3-10-09 (updated)
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	NDA Reg Filing Rvw: 2-27-09
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None
• Outgoing communications *(if located elsewhere in package, state where located)*	Included
• Incoming submissions/communications	3-3-09; 3-27-09
❖ Postmarketing Commitment (PMC) Studies	☐ None

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	Included
• Incoming submission documenting commitment	3-27-09
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	9/24/08 Telecon; 8/6/08 Telecon
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable 2/11/09
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable 3/17/09
• Regulatory Briefing *(indicate date)*	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 4/3/08
• EOP2 meeting *(indicate date)*	☐ No mtg 11/13/08
• Other (e.g., EOP2a, CMC pilot programs)	None
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 3-30-09
Division Director Summary Review *(indicate date for each review)*	☐ None 3-27-09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 3-27-09
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	3-27-09
• Clinical review(s) *(indicate date for each review)*	3-27-09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	See MOR
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See MOR
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None QT review; 11-19-08
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	☐ None 3-19-09
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 2-18-09
Clinical Microbiology ☒ None	

[5] Filing reviews should be filed with the discipline reviews.

❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 3-18-09
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 3-18-09
Statistical Review(s) *(indicate date for each review)*	☐ None 3-18-09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 3-9-09
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 3-9-09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 3-24-09
• Supervisory Review(s) *(indicate date for each review)*	☐ None 3-23-09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 3-12-09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☐ None 12-2-03 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 3-26-09
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 3-18-09
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 3-18-09; 3-5-09
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	3-20-09 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 1-8-09
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC review
☐ Review & FONSI *(indicate date of review)*	

☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 2-23-09 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	 Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A 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/

Christy Cottrell
4/1/2009 02:19:50 PM

MEMORANDUM OF TELECON

DATE: March 30, 2009

APPLICATION NUMBER: NDA 22-334, Afinitor (everolimus) tablets 5 mg and 10 mg

BETWEEN:

Name: Sibylle Jennings, PhD
Phone: (862) 778-1196
Representing: Novartis Pharmaceuticals Corporation

AND

Name: Christy Cottrell
Division of Drug Oncology Products, HFD-150

SUBJECT: Confirmation of sponsor receipt of action letter

I emailed Sibylle Jennings a copy of the official action letter at sibylle.jennings@novartis.com. At 1:36 pm EST, Dr. Jennings called and confirmed receipt of the action letter.

Christy Cottrell
Regulatory Project Manager

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

/s/

Christy Cottrell
3/30/2009 03:22:28 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	March 18, 2009
APPLICATION:	NDA 22-334
DRUG NAME:	Afinitor (everolimus) tablets 5 mg and 10 mg
TYPE OF MEETING:	Telecon regarding Adverse Reactions section of the PI
SPONSOR:	Novartis Pharmaceuticals Corporation
MEETING CHAIR:	Qin Ryan, MD, Clinical Reviewer
MEETING RECORDER:	Christy Cottrell, Regulatory Project Manager

FDA ATTENDEES:

Robert Justice, MD, Director, Division of Drug Oncology Products
Ellen Maher, MD, Clinical Team Leader
Qin Ryan, MD, Clinical Reviewer
Christy Cottrell, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

David Lebwohl, MD, Clinical
Andrea Kay, MD, Clinical
Peter Berry, MD, Clinical
Tomas Haas, PhD, Statistics
Sophie Jauffret, PhD, Statistics
Joseph Posluszny, PhD, Drug Regulatory Affairs
Sibylle Jennings, PhD, Drug Regulatory Affairs
Lynne McGrath, PhD, Drug Regulatory Affairs
Nina Gutman, PhD, Drug Regulatory Affairs

BACKGROUND:

The Division requested this telecon to clarify discrepancies in the Adverse Events numbers in the package insert.

DISCUSSION:

Dr. Ryan explained to the applicant that she was unable to reproduce their numbers using their treatment emergent adverse event data (specifically for Table 1 in the Full Prescribing Information) and asked for clarification on the evaluation criteria and search terms used to derive those numbers. The applicant stated that Table 1 only includes adverse events with investigator assessment of Afinitor-related causality. In addition, the applicant noted that they used preferred search terms to derive the numbers with 3 exceptions: a) stomatitis and b) pneumonitis and, c) infections, which were searched under the broader terms within each term's MedDRA SOC for clinical notability. The applicant explained that these search criteria were outlined in the footnote to Table 1, as below.

a. Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

b Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

c Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

The Division asked the applicant to perform an analysis regardless of attribution using the same search strategy that was used for Table 1. The applicant agreed to provide the analysis result by the end of the day.

Christy Cottrell
Regulatory Project Manager

Concurrence:

Qin Ryan, MD
Clinical Reviewer

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

/s/

Christy Cottrell
3/25/2009 01:32:48 PM

Qin Ryan
3/27/2009 09:26:25 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 17, 2009
APPLICATION: NDA 22-334
DRUG NAME: Afinitor (everolimus) tablets
TYPE OF MEETING: Pre-Approval Safety Conference
MEETING CHAIR: Qin Ryan, MD, Clinical Reviewer
MEETING RECORDER: Christy Cottrell, Regulatory Project Manager

FDA ATTENDEES:
Richard Pazdur, MD, Director, Office of Oncology Drug Products (OODP)
Tony Murgo, MD, Associate Director, OODP
Robert Justice, MD, Director, Division of Drug Oncology Products
V. Ellen Maher, MD, Clinical Team Leader
Qin Ryan, MD, Clinical Reviewer
Somesh Chattopadhyay, PhD, Statistical Reviewer
Shenghui Tang, PhD, Statistical Team Leader
Julie Bullock, PharmD, Actg Clinical Pharmacology Team Leader/Clin Pharmacology Reviewer
Haleh Saber, PhD, Pharm/Tox Team Leader
Shwu-Luan Lee, PhD, Pharm/Tox Reviewer
Albert Deisseroth, MD, Clinical Reviewer
Sandra Griffiths, Regulatory Project Manager, Office of Safety and Epidemiology
Iris Masucci, PharmD, BCPS, Labeling Reviewer, SEALD, OSE
Keith Olin, PharmD, Regulatory Reviewer Officer, DDMAC
Jeanne Perla, PhD, Risk Management Analysis, DRISK, OSE
Robert Pratt, PharmD, Postmarketing Safety Evaluator, OSE
Nancy Carothers, RN, BA, Patient Product Information Reviewer, OSE
Suzanne Berkman, PharmD, Senior Risk Mgmt Analyst and Acting Team Leader, DRISK, OSE

BACKGROUND: NDA 22-334 for Afinitor (everolimus) tablets was submitted on June 30, 2008. Originally, this application was designated as a Priority review with a PDUFA due date of December 30, 2008. However, a major chemistry amendment was received in early December 2008 which extended the clock. The new PDUFA date became March 30, 2009. Since this application is a New Molecular Entity, a Pre-Approval Safety Conference is required.

DISCUSSION POINTS:
Dr. Ryan explained that the primary safety concern with this product is pneumonitis which occurred at a rate of 14% in the pivotal study.

Dr. Perla stated that Novartis believes that the incidence of pneumonitis does not warrant a RiskMap. The Division agreed, provided that pneumonitis is followed closely during post-marketing surveillance. OSE agreed to provide expedited reports to the Division for observations of pneumonitis in the post-marketing setting.

Christy Cottrell
Regulatory Project Manager

Concurrence:
Qin Ryan, MD
Clinical Reviewer

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

/s/

Christy Cottrell
3/24/2009 11:56:04 AM

From: Cottrell, Christy L.
Sent: Thursday, March 19, 2009 10:39 AM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Post-Marketing Commitment

Importance: High

Sibylle,

Please refer to your NDA 22-334 for Afinitor. Below is a draft Post-Marketing Commitment (PMC). Please review and provide dates where indicated. Your commitment to perform this PMC (exactly as worded) will need to be submitted officially the NDA.

- Submit the final, per-protocol overall survival analysis of study C2240 which was to be conducted 2 years after randomization of the last patient.

  Protocol Submission:
  Study Start:
  Final Report Submission:

Let me know if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

---

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

/s/

Christy Cottrell
3/23/2009 03:20:27 PM
CSO

From: Mesmer, Deborah
To: Mesmer, Deborah;
Subject: RE: question re. NDA 22334- CMC IR 030909
Date: Monday, March 09, 2009 1:13:54 PM

The following comment was reviewed by Ravi Kasliwal (3/9/09) and Terry Ocheltree (3/6/09).

From: Mesmer, Deborah
Sent: Monday, March 09, 2009 1:07 PM
To: 'jane.xiang@novartis.com'
Subject: RE: question re. NDA 22334- CMC IR 030909

Dear Dr. Xiang,

A CMC request for clarification follows as conveyed to you today by phone. Please submit your response to the NDA with a courtesy copy to me.

Sincerely,

Debbie Mesmer

Deborah Mesmer
Regulatory Health Project Manager
FDA/CDER
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment III and Manufacturing Science
301-796-4023
deborah.mesmer@fda.hhs.gov

Information Request: NDA 22-334

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afinitor and your amendment dated January 20, 2009.

We have the following comment and request for clarification.

You have indicated that in the test procedure 53501.02 used for identification, assay and quantitation of degradation products by HPLC, the reporting limit for impurities is [redacted] Clarify and confirm in the quantitation of total degradation products that all the impurity / degradation products above the Limit of Quantitation (LOQ) are considered and reported. b(4)

Please amend your application with your response.

From: jane.xiang@novartis.com [mailto:jane.xiang@novartis.com]
Sent: Monday, March 09, 2009 12:42 PM
To: Mesmer, Deborah
Subject: question re. NDA 22334

Dear Debbie,

Per our discussion, this is to confirm that it is acceptable to us for you to send via email the CMC question that we just discussed over the phone with respect to NDA 22334. Thank you very much.

Best regards,

Jane Xiang, Ph.D.
Global Regulatory CMC
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
Phone: +1 (862) 778-8741
Email : jane.xiang@novartis.com

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

/s/

Deborah M Mesmer
3/16/2009 02:06:20 PM
PROJECT MANAGER FOR QUALITY

Cottrell, Christy L.

From: Gershon, Sharon
ent: Wednesday, March 11, 2009 12:11 PM
To: Purohit-Sheth, Tejashri; Cottrell, Christy L.
Subject: RE: Addendum review for NDA 22-334 (Afinitor)

Christy,

I have not yet received the EIR (inspectional summary) from the Camilla Porta site in Italy. However, I completed a Clinical Inspection Summary that was entered into DFS on approximately Feb 19, 2009,
and this CIS contained a summary of the Porta inspection based on a faxed FDA-483, and discussions with the field investigator. I do not expect that this summary will have any significant changes after I review the
EIR, and therefore, there will be no addendum to the CIS. If you have further questions, let me know.

Sharon

From: Purohit-Sheth, Tejashri
Sent: Monday, March 09, 2009 2:17 PM
To: Cottrell, Christy L.; Gershon, Sharon
Subject: FW: Addendum review for NDA 22-334 (Afinitor)

Hi Christy,

The assigned reviewer for this application is Sharon Gershon.

Sharon, can you please give us a status update on the last foreign inspection? Have you received the EIR, or any other preliminary communication? Thanks.

ejashri

From: Cottrell, Christy L.
Sent: Monday, March 09, 2009 2:15 PM
To: Purohit-Sheth, Tejashri
Cc: Ryan, Qin
Subject: Addendum review for NDA 22-334 (Afinitor)

Tejashri-

Has an addendum review been completed yet for NDA 22-334 (Afinitor)? We have a preliminary review, but there was still 1 foreign site still pending. If you've already completed the review, just let me know and I will pull it out of DFS.

Thanks,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

9♣♦9♥☻9☺9P♣☺┐☺ ☺⁞↕KKTB⁞⁞‼☺KKSB▒ 2+K⁞⁞dRBàìì↔⁞⁞ûKRX⁞⁞Ç↔Y¥TX⁞⁞☺⁞⁞☺ÄY▓SX⁞⁞☺⁞⁞☺ÄY++++++++st

From: Cottrell, Christy L.
Sent: Monday, March 09, 2009 9:18 PM
To: 'sibylle.jennings@novartis.com'
Subject: RE: NDA 22-334 for Afinitor: CMC request for information - Advice needed on how to proceed with outstanding final response to blister comments

Sibylle,

I discussed these outstanding CMC items with the reviewer, and he has stated that the blister pack is acceptable (so you can ignore comment 2a) and the NDC explanation is acceptable. Please submit your response officially to the NDA.

Let me know if you have any questions.

Regards,
Christy

! #$ sibylle.jennings@novartis.com [mailto:sibylle.jennings@novartis.com]
le .j y Thursday, March 05, 2009 3:09 PM
ni y Cottrell, Christy L.
lg @evj y Re: NDA 22-334 for Afinitor: CMC request for information - Advice needed on how to proceed with outstanding final response to blister comments

Dear Christy,

I am contacting you to ask for advice how we can best proceed with regard to the 2 comments on the blister label (2.b) and 2.c)), to which we did not yet officially respond.
We sent you via FedEx a sample of the actual printed blisters to allow a review of the appearance of the different colors when printed on the blister foil. and you confirmed to have received the FedEx package last Thursday afternoon.
In my e-mail from February 22, I also gave some explanation for the 'NDC' number that was found missing according to comment 2.c, I copied this explanation below for your convenience:

C) 'Include NDC# on sample blister packs also.'
Novartis response: At the moment the sample blister contains a number which is not identified as 'NDC' number, since it is strictly speaking not an NDC number which we have for our drug samples, but rather a tracking number.

Did you receive any feedback from the CMC reviewer yet whether his concerns still exist, or can you estimate when you may receive his

feedback? I feel a little bit uncomfortable that we did not submit an official response to these 2 comments on the blister label yet, and would appreciate your advice how best to move forward. Thank you very much in advance for your help in this matter.

I hope the labeling meeting went well today?

Best regards,
Sibylle

Sibylle Jennings
Novartis Pharmaceuticals Corporation
PH, Dev - Oncology DRA II
USEH, Building 105 Open Space 1W380A
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA
Phone: +1 862 7781196
Cell: +1 862 596 4679
Email : sibylle.jennings@novartis.com

"Cottrell, Christy L." <Christy.Cottrell@fda.hhs.gov>
02/19/2009 03:45 PM

Please respond to
christy.cottrell@fda.hhs.gov

To
sibylle.jennings@novartis.com
cc

Subject

NDA 22-334 for Afinitor: CMC request for information

Sibylle,
Please refer to your pending NDA 22-334 for Afinitor. Below are two additional requests for information (one from CMC, one from clinical).
CMC
1. Provide calculations that have led to your conclusion that the concentration of the active moiety, everolimus, at the point of entry into the aquatic environment will be significantly less than 1 ppb.

2. Provide updated blister pack and carton pack labels that incorporate the following: b(4)

Clinical
This request is regarding your latest amendment, information that would support Tables 2-2 and 2-3. Please provide the list of patients who were counted dead or having PD in safety report but not in efficacy report and vice-versa.
Since we are nearing the deadline for this application, a rapid response is appreciated.
Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
(301.796.4256 (phone) ● 301.796.9845 (fax) | *
christy.cottrell@fda.hhs.gov

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

/s/

Christy Cottrell
3/10/2009 10:27:58 AM
CSO

From: Cottrell, Christy L.
Sent: Friday, March 06, 2009 6:22 PM
To: 'sibylle.jennings@novartis.com'
Subject: Agenda for 3/9/09 Meeting with FDA

Importance: High

Attachments: efficacy_vs_safety_PDdeath2.rtf; 3-6-09 agenda for mtg.doc

Sibylle,

Attached is a document outlining the topics we would like to discuss on Monday, 3/9/09. In this document, we ask you to provide additional analyses. If you are not able to complete these analyses by Monday, we would recommend postponing the meeting until the analyses are completed. If you are able to provide these analyses for discussion by Monday, we would like to move the meeting up to a 10:30am start time, rather than 11:00am to give us additional discussion time if needed. We ask that you bring a laptop, projector and all of your data for discussion. In addition, your statistical experts should be available either in person or by phone. Alternatively, if you believe the discrepancies are adequately addressed through the new analyses, you may simply provide the analyses for our review and forego a meeting altogether.

Please let me know once you have determined whether you will be able to provide the requested analyses by Monday and I will alert my team.

Feel free to contact me if you have any questions.

Regards,
Christy

efficacy_vs_safety_PDdeath2.rt... 3-6-09 agenda for mtg.doc (39 ...

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

We refer to our clinical information request sent on March 2, 2009 and your response submitted on March 3, 2009. We cannot reconcile the discrepancies between the efficacy PFS events (either based on central review or based on investigator's assessment) and PD or death as a reason for study discontinuation.

We also refer to your response dated February 18, 2009 to another information request. You have stated possible reasons for the discrepancies in that document. However, that response is not sufficient to reconcile the above-mentioned discrepancies. See attached tables.

Per our guidance document, (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics), please analyze PFS using the following censoring rules for each of the investigator and central review progression assessments:

Event = Progression or death

Censor at last assessment with no documented progression if, (1) no documented progression or death at data cut-off date; (2) discontinued treatment, including due to toxicity; (3) changed therapy or added non-protocol therapy; (4) lost-to-follow-up; (5) withdrew consent; (6) event observed after more than one missing assessment.

By early next week, please provide us with these analyses using the above rules for both central review assessments and investigator assessments. Also provide accompanying datasets and SAS program.

By the end of next week or sooner, please provide a patient by patient listing and summary with detailed reason for discrepancy between PFS event (based on both central review and investigator's assessment) and reason for discontinuation for each patient.

	Oct 15 2007 cut-off (N = 410)					
	Disposition		**IRC**		**INV**	
	R (n=272)	**P (n=138)**	**R (n=272)**	**P (n=138)**	**R (n=272)**	**P (n=138)**
Death (%)	7 (2.6)	3 (2.2)	16 (5.9)	8 (5.8)	14 (5.1)	7 (5.1)
Progression (%)	85 (31.3)	100 (72.5)	85 (31.3)	82 (59.4)	97 (36.7)	98 (71.0)
	Feb 25 2008 cut-off (N = 416)					
	Disposition		**IRC**		**INV**	
	R (n=277)	**P (n=139)**	**R (n=277)**	**P (n=139)**	**R (n=277)**	**P (n=139)**
Death (%)	7 (2.5)	4 (2.9)	21 (7.6)	8 (5.8)	18 (6.5)	8 (6.8)
Progression (%)	137 (49.5)	124 (89.2)	134 (48.4)	103 (74.1)	152 (54.9)	121 (87.1)

The FREQ Procedure

Table 1: Cross-tabulation of Discontinuation Reason from Patient Disposition and Type of PFS Event/Censoring as Determined by Independent Radiology – All Patients

Table of DCNRSN1C by PFS1_TYP				
DCNRSN1C(Reason for discontinuation of treatment)	PFS1_TYP(Progression-free survival type)			
Frequency	Death	PD	Censor	Total
.	0	8	9	17
Adverse Event(s)	5	20	13	38
Abnormal laboratory value(s)	0	1	0	1
Protocol violation	1	0	2	3
Subject withdrew consent	1	5	9	15
Lost to follow-up	0	1	3	4
Administrative problems	0	1	1	2
Death	8	3	0	11
Disease progression	14	179	68	261
Final primary analysis	0	19	45	64
Total	29	237	150	416

The FREQ Procedure

Table 2: Cross-tabulation of Discontinuation Reason from Patient Disposition and Type of PFS Event/Censoring as Determined by Independent Radiology – RAD001 Arm

Table 1 of DCNRSN1C by PFS1_TYP				
Controlling for trt=RAD001				
DCNRSN1C(Reason for discontinuation of treatment)	PFS1_TYP(Progression-free survival type)			
Frequency	Death	PD	Censor	Total
.	0	6	7	13
Adverse Event(s)	5	18	13	36
Abnormal laboratory value(s)	0	1	0	1
Protocol violation	1	0	1	2
Subject withdrew consent	0	4	9	13
Lost to follow-up	0	1	3	4
Administrative problems	0	1	1	2
Death	5	2	0	7
Disease progression	10	82	45	137
Final primary analysis	0	19	43	62
Total	21	134	122	277

The FREQ Procedure

Table 3: Cross-tabulation of Discontinuation Reason from Patient Disposition and Type of PFS Event/Censoring as Determined by Independent Radiology – Placebo Arm

Table 2 of DCNRSN1C by PFS1_TYP				
Controlling for trt=Placebo				
DCNRSN1C(Reason for discontinuation of treatment)	PFS1_TYP(Progression-free survival type)			
Frequency	Death	PD	Censor	Total
.	0	2	2	4
Adverse Event(s)	0	2	0	2
Abnormal laboratory value(s)	0	0	0	0
Protocol violation	0	0	1	1
Subject withdrew consent	1	1	0	2
Lost to follow-up	0	0	0	0
Administrative problems	0	0	0	0
Death	3	1	0	4
Disease progression	4	97	23	124
Final primary analysis	0	0	2	2
Total	8	103	28	139

The FREQ Procedure

Table 4: Cross-tabulation of Discontinuation Reason from Patient Disposition and Type of PFS Event /Censoring as Determined by Investigator – All Patients

Table of DCNRSN1C by PFS1_TYP				
DCNRSN1C(Reason for discontinuation of treatment)	PFS1_TYP(Progression-free survival type)			
Frequency	Death	PD	Censor	Total
.	0	4	13	17
Adverse Event(s)	9	13	16	38
Abnormal laboratory value(s)	0	1	0	1
Protocol violation	1	0	2	3
Subject withdrew consent	2	4	9	15
Lost to follow-up	1	0	3	4
Administrative problems	0	0	2	2
Death	10	1	0	11
Disease progression	3	248	10	261
Final primary analysis	0	2	62	64
Total	26	273	117	416

The FREQ Procedure

Table 5: Cross-tabulation of Discontinuation Reason from Patient Disposition and Type of PFS Event /Censoring as Determined by Investigator – RAD001 Arm

Table 1 of DCNRSN1C by PFS1_TYP				
Controlling for trt=RAD001				
DCNRSN1C(Reason for discontinuation of treatment)	PFS1_TYP(Progression-free survival type)			
Frequency	Death	PD	Censor	Total
.	0	4	9	13
Adverse Event(s)	8	12	16	36
Abnormal laboratory value(s)	0	1	0	1
Protocol violation	1	0	1	2
Subject withdrew consent	1	3	9	13
Lost to follow-up	1	0	3	4
Administrative problems	0	0	2	2
Death	6	1	0	7
Disease progression	1	129	7	137
Final primary analysis	0	2	60	62
Total	18	152	107	277

The FREQ Procedure

Table 6: Cross-tabulation of Discontinuation Reason from Patient Disposition and Type of PFS Event /Censoring as Determined by Investigator – Placebo Arm

Table 2 of DCNRSN1C by PFS1_TYP				
Controlling for trt=Placebo				
DCNRSN1C(Reason for discontinuation of treatment)	PFS1_TYP(Progression-free survival type)			
Frequency	Death	PD	Censor	Total
.	0	0	4	4
Adverse Event(s)	1	1	0	2
Abnormal laboratory value(s)	0	0	0	0
Protocol violation	0	0	1	1
Subject withdrew consent	1	1	0	2
Lost to follow-up	0	0	0	0
Administrative problems	0	0	0	0
Death	4	0	0	4
Disease progression	2	119	3	124
Final primary analysis	0	0	2	2
Total	8	121	10	139

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

/s/

Christy Cottrell
3/10/2009 10:27:04 AM
CSO

From: Cottrell, Christy L.
Sent: Thursday, March 05, 2009 8:40 PM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Meeting/Telecon request

Importance: High

Sibylle,

The team has decided that a meeting with Novartis is needed to discuss some outstanding issues. We would like to have this discussion on **Monday, 3/9/09 at 11:00am EST**, if your team is available. This meeting can be either face-to-face or a teleconference- we'll leave that decision up to you. The primary discussion topics will be clinical and statistical in nature, but I will ask the CMC reviewer to attend as well, so we can hopefully wrap up those outstanding issues at the same time.

Let me know if this time works for you and your team.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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

/s/

Christy Cottrell
3/10/2009 10:26:17 AM
CSO

From: Cottrell, Christy L.
Sent: Monday, March 02, 2009 10:41 AM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Clinical Information Request

Sibylle,

Please refer to your NDA 22-334 for Afinitor. Below is a Clinical Information request.

Please provide data to fill in the blank cells in the table below.

Disposition	Second Interim Analysis Data cut-off: 15-Oct-2007		Safety Update Data cut-off: 28-Feb-2008	
	Everolimus N=272 (%)	Placebo N=138 (%)	Everolimus N=277 (%)	Placebo N=139 (%)
Ongoing	**140 (52.0)**	**29 (21.5)**	**75 (27.4)**	**6 (4.4)**
Discontinued	**129 (48.0)**	**106 (78.5)**	**199 (72.6)**	**131 (95.6)**
Cross over	n/a	80	n/a	109
Main reason for discontinuation				
Disease progression	85 (31.3)	82 (59.4)	134 (48.4)	103 (74.1)
Death	16 (5.9)	8 (5.8)	21 (7.6)	8 (5.8)
Adverse event(s)				
Patient withdrew consent				
Lost to follow-up				
Protocol violation				
Administrative problems				
Abnormal laboratory value(s)				

Let me know if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) » 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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

/s/

Christy Cottrell
3/2/2009 10:44:06 AM
CSO

From: Cottrell, Christy L.
Sent: Friday, February 27, 2009 3:14 PM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Timeline for PMRs

Sibylle,

Please refer to your NDA 22-334 for Afinitor. We need you to provide timelines for the following Post-Marketing Requirements.

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

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

2. Conduct a trial in patients with severe hepatic impairment (Child Pugh Class C). This study need not be conducted in patients with cancer and a single dose evaluation will be appropriate. The protocol should be submitted prior to initiation for review and concurrence.

Protocol Submission:
Trial Start Date:
Final Report Submission:

Let me know if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

---

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

/s/

Christy Cottrell
2/27/2009 03:16:26 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-334 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Afinitor
Established Name: everolimus
Strengths: 5 mg and 10 mg Tablets

Applicant: Novartis Pharmaceutics Corp
Agent for Applicant (if applicable):

Date of Application: June 27, 2008
Date of Receipt: June 30, 2008
Date clock started after UN:
Date of Filing Meeting: August 7, 2008
Filing Date: August 29, 2008
Action Goal Date (optional): User Fee Goal Date: December 30, 2008

Indication(s) requested: Treatment of advanced renal cell carcinoma

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☐ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☐
     This application is: All electronic ☒ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☒
     Combined NDA and CTD formats ☐

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format?

     Additional comments:

  3. This application is an eCTD NDA. YES ☒
     If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

     Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☒

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 66,279

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) October 25, 2004, January 12, 2006, November 13, 2008 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 7, 2008

NDA #: 22-334

DRUG NAMES: Afinitor

APPLICANT: Novartis Pharmaceuticals Corp

BACKGROUND: Submitted for treatment for advanced renal cell CA

ATTENDEES: R.Justice, Director, A.Ibrahim, MOTL, Q.Ryan, MO, R.Kasiwal, CMC Reviewer, S.Pope, PAL, H.Saber, PTTL, L.Lee, PT reviewer, J.Bullock, Clin Pharm reviewer, B.Booth, DD, Clin Pharm, R.Sridhara, Stats TL, S.Chattopadhyay, stats reviewer, M.Vialpando for D.Woody, RPM

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Q. Ryan
Secondary Medical:	A. Ibrahim
Statistical:	S. Chattopadhyay
Pharmacology:	S. Tang
Statistical Pharmacology:	N/A
Chemistry:	R. Kasiwali
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	J. Bullock
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	
OPS:	N/A
Regulatory Project Management:	A. Kacuba
Other Consults:	OSE, DDMAC

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY	N/A ☒	FILE ☐	REFUSE TO FILE ☐
STATISTICS	N/A ☐	FILE ☒	REFUSE TO FILE ☐
BIOPHARMACEUTICS		FILE ☒	REFUSE TO FILE ☐
• Biopharm. study site audits(s) needed? YES			☐ NO ☒
PHARMACOLOGY/TOX	N/A ☐	FILE ☒	REFUSE TO FILE ☐
• GLP audit needed?			YES ☐ NO ☒
CHEMISTRY		FILE ☒	REFUSE TO FILE ☐
• Establishment(s) ready for inspection?			YES ☒ NO ☐
• Sterile product?			YES ☐ NO ☒
If yes, was microbiology consulted for validation of sterilization?			YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☒ Convey document filing issues/no filing issues to applicant by Day 74.

Alice Kacuba
Regulatory Project Manager

Note: At the time of filing, the application appeared to be complete and no review issues identified. Due to workload, I never sent a 74 day letter. I communicated in a phone call that it was "no issues identified". However, several months into the review, the clinical, stats and clin Pharm reviews noted numerous things missing. Numerous Information Requests were sent. The review clock was later extended due a major amendment.

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

/s/

Alice Kacuba
2/27/2009 12:44:35 PM
CSO

From: Cottrell, Christy L.
Sent: Tuesday, February 24, 2009 2:59 PM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Statistical request for information

Sibylle,

Please refer to your pending NDA 22-334 for Afinitor. Below is a request for additional information from the statistical reviewer.

1. We could not find the Independent Data Monitoring Committee (IDMC) charter for study C2240 in the submission. Please indicate where it is located in the submission. If you have not submitted it with the application, please submit it.

2. Please submit the IDMC report and meeting minutes for both interim analyses of study C2240.

3. On pages 8891 and 8892 in Appendix 16.1.9 of the study report for study C2240 there were several references to "Table 4 on p.16 of the Post-text supplement 1 of the study protocol/ MAP" which we could not find. The link takes us to the protocol post-text supplement which has only 9 pages and has only tables 1-1, 1-2 and 1-3. Please provide "Table 4" that pages 8891 and 8892 referred to.

Feel free to contact me if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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

/s/

Christy Cottrell
2/26/2009 02:25:47 PM
CSO
Sent to sponsor on 2/24/09

From: Cottrell, Christy L.
Sent: Friday, February 20, 2009 10:24 AM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Response to phone message

Sibylle-

I forwarded your inquiry to the CMC reviewer regarding the labels. He said he reviewed the January 12 submission, and feels that you've reasonably addressed item A, however, item B has not been adequately addressed yet.

I will discuss scheduling a telecon for next week with the team during Monday morning's labeling meeting. If they agree with scheduling a telecon, I'll be in touch on Monday to set up a mutually agreeable time.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

---

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

/s/

Christy Cottrell
2/20/2009 10:27:10 AM
CSO

From: Cottrell, Christy L.
Sent: Thursday, February 19, 2009 3:45 PM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: CMC request for information

Sibylle,

Please refer to your pending NDA 22-334 for Afinitor. Below are two additional requests for information (one from CMC, one from clinical).

CMC

1. Provide calculations that have led to your conclusion that the concentration of the active moiety, everolimus, at the point of entry into the aquatic environment will be significantly less than 1 ppb.

2. Provide updated blister pack and carton pack labels that incorporate the following:

   a.

   b.

   c.

   d.

   e.

b(4)

Clinical

This request is regarding your latest amendment, information that would support Tables 2-2 and 2-3. Please provide the list of patients who were counted dead or having PD in safety report but not in efficacy report and vice-versa.

Since we are nearing the deadline for this application, a rapid response is appreciated.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

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

/s/

Christy Cottrell
2/19/2009 03:48:50 PM
CSO

MEMORANDUM
HUMAN SERVICES

DEPARTMENT OF HEALTH AND

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE:	February 18, 2009
TO:	Alice Kacuba, Regulatory Project Manager Qin Ryan, Medical Officer Division of Cardio-Renal Drug Products
FROM:	Sharon K. Gershon, Pharm.D. Good Clinical Practice Branch 2 Division of Scientific Investigations
THROUGH:	Tejashri Purohit-Sheth M.D. Branch Chief Good Clinical Practice Branch 2 Division of Scientific Investigations
SUBJECT:	Evaluation of Clinical Inspections.
NDA:	22-334
APPLICANT:	Novartis Pharmaceuticals 1 Health Plaza East Hanover, New Jersey 07936
DRUG:	Afinitor (everolimus) tablets
NME:	Yes

THERAPEUTIC CLASSIFICATION: Standard/Priority Review

INDICATION: ——— renal cell carcinoma (RCC) b(4)

CONSULTATION REQUEST DATE: August 5, 2008

DIVISION ACTION GOAL DATE: February 20, 2009

PDUFA DATE: March 20, 2009

I. BACKGROUND:

Novartis Pharmaceuticals submits this NDA for the evaluation of Afinitor® (everolimus) in the treatment of patients with ——— renal cell carcinoma. A single study was submitted in support of the proposed indication: b(4

Protocol: "RAD001C2240: "A randomized, double-blind, placebo-controlled, multicenter phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed after treatment with VEGF receptor tyrosine kinase inhibitor therapy."

Everolimus (RAD001) is an orally administered inhibitor of the mammalian target of rapamycin (mTOR), a therapeutic target for metastatic renal cell carcinoma. RAD001 selectively inhibits mTOR, a key protein kinase present in all cells which regulates cell growth, proliferation, and survival. MTOR is mainly activated via the P13 kinase pathway. Mutations in these components may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers.

Renal cell carcinoma (RCC) is the most common form of kidney cancer arising from the renal proximal tubal epithelium. Renal cell carcinoma is characterized by a distinct clear or granular cell appearance visible by light microscopy. Alternatively, it is known as clear-cell cancer or renal adenocarcinoma. Initial treatment is surgery. If it is only in the kidneys, which is about 40% of cases, it can be cured roughly 90% of the time with surgery. It is resistant to radiation therapy and chemotherapy, although some cases respond to immunotherapy. Targeted cancer therapies such as sunitinib or sorafenib, have improved the outlook for RCC, although they have not yet demonstrated improved survival. Sunitinib—an oral, small-molecule, multi-targeted (RTK) inhibitor—and sorafenib both interfere with tumor growth by inhibiting angiogenesis as well as tumor cell proliferation. Both agents are classified as Vascular Endothelial Growth Factor-receptor (VEGFr) tyrosine kinase inhibitors (TKI).

The study had five phases: screening/baseline; blinded treatment; open-label RAD001, follow-up and the extension portion of the study. The first day of blinded treatment began on Day 1, Cycle 1. Each treatment Cycle lasted 28 days. There was no fixed duration of treatment, thus, patients were permitted to continue on blinded treatment until the occurrence of tumor progression determined by the local radiologist or until unacceptable toxicity, or death or discontinuation from the study for any other reason. Patients who discontinued treatment for any reason had a follow-up visit which was scheduled 28 days after the last dose of the study drug. Commonly reported adverse events included stomatitis, rash, fatigue, and pneumonitis.

Patients with metastatic RCC which had progressed despite treatment with VEGFr TKIs (sunitinib, sorafenib, or both), were randomly assigned in a two to one ratio to receive everolimus 10 mg once daily (n=272) or placebo (n=138), in conjunction with best supportive care (BSC). The primary endpoint was progression-free survival (PFS), assessed radiologically, and via a blinded, independent central review. Secondary outcome measures included overall survival assessed by monthly overall survival assessments; tumor response rates assessed by tumor assessments via CT scans or MRIs of chest, abdomen and pelvis every

8 weeks; the patient's overall quality of life assess by EORTC-QLQ- C30; safety assessed by Pulmonary Function Tests, vital signs, chest X-rays, and laboratory assessments.

Three clinical investigator sites (1 domestic, 2 foreign) were inspected for approval of this NDA. The basis of the site selection was the number of enrolled patients and PFS (primary endpoint) events. The Review Team was interested to learn whether the AEs, disease evaluations and progression events documented in medical records are consistent with the CRFs. In addition, they wished to identify any violation of enrollment criteria in the medical records that is not noted on CRFs. This information was reviewed and corroborated during the inspections.

In addition to the 3 clinical investigator inspections, DSI conducted a sponsor inspection, as is typically done for a New Molecular Entity (NME). Results from these inspections are posted below.

II. RESULTS (by Site):

Name of CI, or Sponsor Location	Site # and # of Subjects	Inspection Dates	Final Classification
Robert Motzer, M.D. Memorial Sloan-Kettering Cancer Center 1275 New York Avenue New York, NY 10021	Site 513 21 subjects (E =12, P=9)	10/27 to 10/30/2008	NAI
Stephanie Oudard, M.D. Hopital Georges Pompidou 20, rue Leblanc Paris 75015 France	Site #606 30 subjects (E=24, P=6)	12/08 to 12/12/2008	VAI
Camillo Porta Center IRCCS San Matteo University Hospital Piazzale Golgi, 19 Pavia 1027100 Italy	Site #756 24 subjects (E=21, P=3)	12/15 to 12/19/2008	Pending
Novartis Pharmaceuticals Oncology Business Unit 180 Park Avenue Florham Park, New Jersey 01932-0675	Sponsor inspection	10/29 to 11/18/2008	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.
E = Everolimus
P = Placebo

1. **Robert Motzer, M.D.** (Site 513), Memorial Sloan-Kettering Cancer Center, 1275 New York Avenue, New York, NY 10021

What was inspected: A total of 28 subjects were screened for the study; a total of 21 subjects were randomized. Of the 21 patients randomized, 10 were reviewed in depth, and an additional 5 subjects (15 subjects total) were reviewed for accurate informed consent documentation, and initial dates of dosing. The inspection compared case report forms with source documents including hospital charts and medical records, and compared them with the data listings provided from the sponsor, for all 21 subjects. The primary and secondary endpoints were reviewed and verified for all subjects. The inspection reviewed inclusion and exclusion criteria, test article accountability records and adverse event reporting for all 21 subjects.

General observations/commentary: The inspection compared date recorded in source records, case report form and sponsor provided data listings for all 21 subjects concerning primary and secondary efficacy endpoints. No discrepancies were noted. The inspection found that all adverse events were accurately documented for all 21 subjects. The inspection found that concomitant therapy and intercurrent illnesses were accurately reported. All subjects were found to have met the study's entrance criteria. There were two discussion points that included missing chest x-rays for two subjects, and two instances where the results of biomarkers were missing. Dr. Motzer was aware of the missing data, and stated that he would perform a file search to locate the missing data. Test article accountability records were reviewed and found to be accurate, and storage conditions for investigational drug were as per protocol. No FDA-483 was issued during the inspection.

Assessment of data integrity: There were no discrepancies between the source documents and data listings from the sponsor, concerning the primary and secondary efficacy endpoints, inclusionary criteria, adverse event reporting, and test article accountability records. No significant recordkeeping or data deficiencies were observed. In general, the data appear acceptable to use in support of this NDA.

2. **Stephane Oudard (Site 606)**, M.D., Hospital Georges Pompidou, 20, rue Leblanc Paris 75015 France

What was inspected? A total of 37 subjects were screened at this site, and 30 subjects were enrolled. A total of 15 subjects continued in the open label study to receive RAD001, and at the time of the inspection, only 5 subjects remained in the open label study. A 100% review of informed consent documents was done; inclusion and exclusion criteria, primary and secondary endpoints were reviewed and corroborated with sponsor's data listings for all subjects. The inspection source data records included medical records, patient notes, radiology reports, and laboratory reports. Medical history and diagnostic reports were written in the French language, and were interpreted with the aid of a translator hired by the sponsor. The inspection reviewed IRB approvals, sponsor and IRB correspondences, financial disclosures, adverse event reports, and compared data listings with source records. The inspection audited

drug accountability records, and other pharmacy records, including correct dosage administration, drug dispensation and returned drug. The inspection reviewed the subject's visit and assessment schedule to ensure all baseline, treatment phase, and follow-up visits were appropriately conducted. The inspection reviewed the patient's assessment of symptoms FKSI-DRS questionnaires and patient's overall Quality of Life assessments EORTC QLQ-C30. Data collected were compared with the data listings provided from the sponsor.

General Observations: A 2-observational FDA-483 was issued: Item 1a) failure to follow the investigational plan, for 2 subjects. Specifically, physical examinations were not conducted on Day 1 of each study Cycle, for 2 subjects, as required by the protocol. For Subject 00003, the physical examination was conducted on July 25, 2007 for Cycle 5 and on November 14, 2007 for Cycle 7, which was 2 days after Day 1; for Subject 00012, the physical examination was conducted on July 5, 2007, 3 days after administration of study medication for Cycle 2
Item 1b) The patient's diary treatment logs were missing in the medical records as part of the source documents. The following subject's logs were missing: Subject 00004 – Cycle 2 diary treatment log; Subject 00006 – Cycle 1 diary treatment log; Subject 00009 – Cycle 2 and 9 diary treatment log; Subject 00017 – Cycle 1, 2, 3, 5 & 6 diary treatment logs.

Item 2) investigational drug disposition records are not adequate with respect to quantity and use by subjects [21 CFR 312.62(a)]. Specifically, the quantity and date of return of the study drug was not accurately documented for 30 of 30 subjects. For example, for Subject 001, the amount or quantity of returned study medication was not recorded and dated by the pharmacist. This pattern was commonly observed across all 30 subjects.

Assessment: The observations were discussed during the inspection with the investigational pharmacist and Principal Investigator, Dr. Oudard. Dr. Oudard sent a written response dated January 23, 2009 to the FDA, in which he acknowledged the observations and promised immediate corrective action. He outlined a corrective action plan to the deficiencies observed during the inspection. He stated, and it was verified that maintaining drug diaries was not a protocol requirement; therefore, this observation does not violate regulatory requirements nor does it impact the data integrity. Dr. Oudard stated that he initiated this procedure so subjects could maintain their own record of drug compliance during the trial. He also states that subjects were terminal, so he considered that compliance was probably very high.

Observation #2 (poor investigational drug disposition records with regard to use and quantity) applied to not maintaining drug accountability for returned study drug medication. According to the field investigator, this lack of drug accountability did not apply to dispensation of study drug, as these records were maintained, and the amount of drug and date dispensed were documented. The field auditor also stated that he verified that subjects received the medication to which they were assigned. The protocol states "the investigator or his/her designee must keep documentation (overall drug accountability log) for the study of tablets administered, tablets used, dates

dispensed and intervals between visits. Compliance will be assessed by the investigator of his/her designee at each visit using pill counts. This information should be captured in the source document at each visit." The pharmacist apologized for his poor study drug record documentation. According to the EIR, the CRA (sponsor monitor) documented the counts for study drug returned to the sponsor; he/she did this during each monitoring visit. The inspection verified that all subjects met inclusionary criteria, that the primary and secondary efficacy endpoints corroborated with the sponsor data listings, and that adverse events were accurately documented and reported. In addition, the inspection verified that all subjects received the correct drug treatment according to their assignment. Based on these last few statements, I consider that the poor drug accountability records are significant in terms of recordkeeping, but do not affect the validity of the data. Therefore, I consider the data as acceptable at this site.

3. **Camillo Porta (Site 756),** Center IRCCS San Matteo, University Hospital, Piazzale Golgi, 19 Pavia 1027100 Italy

a. What was inspected? A total of 26 subjects were screened at this site, and 24 subjects were enrolled. At the time of the inspection 3 subjects remained enrolled in the open-label study. The inspection audited all 24 subject records and verified that the primary and secondary endpoints corroborated with the sponsor's data listings. The inspection reviewed informed consent documents, other source records, including clinic charts, laboratory and radiology reports, adverse events, visits and assessments, and drug accountability records.

Observations: The inspection reviewed all 24 subject records and verified the accuracy of the source records with the sponsor's data listings (sent on CD). Informed consent forms were verified as accurate and completed for all subjects. Source data records were available, including medical records, laboratory reports, and radiology reports. Adverse events were observed to be accurately documented and reported.

A 3-part, one observational FDA-483 was issued for not conducting the investigation according to the investigational plan [21 CFR 312.60]. Specifically:

a) PRO assessments EORTC QLQ-C30 and FKSI Questionnaires were not obtained on Day 1 of every treatment cycle and at discontinuation from the study as required by the protocol. These PRO assessments and questionnaires were not obtained for all 24 subjects randomized into the trial. I spoke with Medical Officer Qin Ryan and she explained the following: "FDA communicated to the applicant in the EOP2 meeting that their PRO tools were neither specific nor fully validated for the study population. Therefore, PRO results were not to be considered as part of the efficacy claim. Following this FDA recommendation, the applicant proposed label did not contain any PRO claims and the PRO results in the NDA will not be part of the clinical review consideration." Further FDA stated that "It is acceptable to use the EORTC measure for exploratory purposes only. ——————————— b(4)

b) Body temperatures as part of vital signs were not obtained for 26 subjects at different visits, as required by the protocol. For example, for Subject 00007, the body

temperatures included in the Vital Signs were not obtained and recorded at screening and at Day 1 of treatment Cycles 1 to 5;
c) Subject 00025 began study trial on August 7, 2007, and was on sunitinib until July 27, 2007, so did not meet the wash-out period of 2 weeks, as required by the protocol for entry into the study.

There were 2 discussion items during the inspection: Karnofsky Performance Scores (KPS) were rated as 100% at screening and during treatment cycles for 90% of subjects. KPS was a functional evaluation used to assess activities of daily living for the subject. The significance of the ratings were as follows: 100 means the subject is normal, which is highly unlikely for this sick population of subjects; 90 = able to carry on normal activities, possibly unlikely for this population; 70 = cares for self, unable to carry on normal activities; 50 = frequent care; 30 = severely disabled; 20 = very sick, supportive care needed; 10 = moribund; 0 = dead. Patients with metastatic illnesses are not likely to be rated as 100% healthy (for the KPS). Concerning this observation, Dr. Porta stated he was not used to using this type of evaluation and used some other daily living performance measurement. An additional discussion item was the investigation found that Subject 021 had identical vital signs and physical examination results at several visits. The inspection noted that all other data appeared accurate, and only this one area (KPS evaluations) was questionable. KPS is not a primary or secondary efficacy endpoint.

Assessment: Observations noted above are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

The Functional Assessment of Cancer Therapy – Disease Related Symptoms (FKSI-DRS) and the EORTC QLQ-C30 questionnaires were used to assess patient reported outcomes. The symptoms covered by the 9-item FKSI-DRS included fatigue, pain, weight loss, dyspnea, cough, fever and hematuria. As stated, the FDA recommended at the EOP2 meeting, that "the PRO results were not to be considered as part of the efficacy claim." Following this FDA recommendation, the applicant proposed label did not contain any PRO claims, and the PRO results in the NDA were not part of the clinical review consideration.

The other noted violations, are unlikely to affect data integrity, and the data is considered acceptable.

4. Sponsor Inspection: Novartis Pharmaceuticals Corporation, Oncology Business Unit 180 Park Avenue, Bldg. — Florham Park, New Jersey 07932-0675

The inspection was conducted at the firm's Florham Park, New Jersey site where the Oncology Business Unit is located (Bldg ———— . The inspection performed a comprehensive evaluation of the Novartis operations for NDA 22-334. The following items were evaluated: organizational responsibility and personnel; administrative structure of the trial; delegation of responsibilities to CROs for the various study- b(4)

related activities; selection and monitoring of clinical investigators for the study; selection of monitors, and monitoring procedures and activities; review of subject records for the 3 audited sites; quality assurance procedures; adverse event reporting procedures; data collection and handling procedures; trial master files; CRF data, including compilation of data; monitoring reports for the 3 inspected sites; protocol waivers and deviations; validation reports for adverse event reporting, statistical programming, and other key management systems; drug integrity and accountability; and financial disclosure and Informed Consent Documents.

An audit of 3 subjects' records per site was conducted, reviewing CRFs to source documentation and sponsor data listings. At the end of the inspection a one-item Form FDA-483 was issued for sponsor transfer of obligations to a Contract Research Organization [21 CFR 312.52(a)]. Specifically, the sponsor's transfer of obligation to a central pharmacy for investigational drug accountability, drug storage and drug shipment to the U.S. clinical investigator sites was not described in writing. A few items were discussed with management but not included in the FDA-438. These included the fact two SAE Follow-up reports were submitted to FDA outside the 15-day timeframe (submitted on days 26 and 43, respectively); that not all Form 1572s were original documents (some were copies); the Informed Consent Document template did not have a separate section listing "whom" the subject could contact for any research-related injury, illness or emergencies, or for questions – this information was provided in the "Compensation for Subject Injury" section; two financial disclosure documents contained illegible dates, and white out was used in the top section of one financial disclosure document.

Assessment: With a few minor discrepancies, the sponsor inspection did not reveal anything unusual that would invalidate the trial results. The data is considered acceptable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Inspectional Summary Report for Site #756 (Porta, Italy) is pending, **and an addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance that are discovered after reviewing the EIR.**

The inspections verified that the efficacy endpoint data at all 3 clinical investigator sites corroborated with the sponsor's data listings. With the exception of Subject 00025 at Site #756 (Porta), the inspection confirmed that subjects met inclusionary criteria. With regard to drug accountability records, the inspection observed that at Site #606 (Oudard), the pharmacist did not document the dates that pills were returned to the site by the subject and the count of the pills. This information was captured by the monitor when returning the pills to the sponsor, as per the protocol. The inspections did not find anything suspicious or unusual with regard to adverse event reporting at any of the sites. DSI recommends the data as reliable for this NDA.

The Inspectional Summary Reports are pending for the 1 foreign clinical investigator site (Porta). This evaluation is based on discussions with the field investigator and faxed FDA-483 for the foreign site. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance that are discovered after reviewing the EIR.

{See appended electronic signature page}

Sharon K. Gershon, GCP Reviewer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

Sharon Gershon
2/18/2009 01:42:46 PM
CSO

Tejashri Purohit-Sheth
2/18/2009 01:44:09 PM
MEDICAL OFFICER

From: Cottrell, Christy L.
Sent: Tuesday, February 17, 2009 2:48 PM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Clinical Information Requests

Sibylle,

Please refer to your pending NDA 22-334 for Afinitor. Below are three clinical requests for additional information.

- Please provide the subgroup PFS analyses by MSKCC prognostics scores and Prior VEGFR-TKI therapies for the February 28, 2008 cut-off date. If you have already submitted these analyses, please indicate the submission date, section and page number.

- Your safety update Table 2-9 indicated 271 events of death (11) and PD (160) at the February 28, 2008 data cut-off, which were different from the efficacy update 266 PFS events of death (29) and PD (137) using the same data cut-off. Similar discrepancies also exist between Table 2-9 and efficacy analyses PFS events for the October 15, 2007 cut-off date. Please explain.

- Please submit subgroup PFS analyses by male and female, older and younger than 65 years, and regions as of February 28, 2008 data cut-off. If you have already submitted these analyses, please indicate submission date, section and page.

Let me know when you expect to submit a response to these inquiries. Also, in follow-up to your phone message of last Friday, we do not have any labeling comments ready to send at this point. We still need additional internal discussion before sending edits to you.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

---

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

/s/

Christy Cottrell
2/17/2009 02:50:31 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **CDER OSE CONSULTS**	FROM: Christy Cottrell, RPM Division of Drug Oncology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2009		NDA 22-334	New NDA	June 30, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Afinitor (everolimus) Tablets	High	NME- 1	March 20, 2009

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This consult request for re-review of the tradename Afinitor Tablets for NDA 22-334. The tradename was originally reviewed by Melina Griffis on August 21, 2008 and the name was found to be acceptable. As the PDUFA date for this application is approaching (March 30, 2009), we are asking for an updated review of the tradename to confirm that it is still acceptable. Package insert and container and carton labels can be found in the EDR.

PDUFA DATE: March 30, 2009
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA 22-334
HFD-150/Division File
HFD-150/RPM
HFD-150/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)

Christy Cottrell, RPM 301-796-4256 WO Bldg 22, Room 2122	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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

/s/

Christy Cottrell
2/11/2009 01:27:09 PM
Consult request for re-review of tradename. Labels in EDR.
PDUFA date 3-30-09.

From: Cottrell, Christy L.
Sent: Monday, February 09, 2009 10:12 AM
To: 'sibylle.jennings@novartis.com'
Subject: NDA 22-334 for Afinitor: Clinical Information Request

Sibylle,

See below for a request for additional information from the clinical reviewer regarding the pending NDA for Afinitor (NDA 22-334).

- Please provide the number of patients that have been crossed over at the Feb 28, 2008 cut-off date. If you already submitted this information, please provide the submission date, section and page that contains it. In addition, please clarify whether the crossover therapy with everolimus was included in the post study therapy data set.

Feel free to call me if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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

/s/

Christy Cottrell
2/9/2009 10:14:02 AM
CSO

From: Cottrell, Christy L.
Sent: Monday, February 02, 2009 1:49 PM
To: 'sibylle.jennings@novartis.com'
Subject: RE: NDA 22-334: Response to Statistical Information Request

Sibylle,

Please refer to your pending NDA 22-334 for Afinitor. See below for an information request from the statistical reviewer:

- We refer to our information request regarding antineoplastic therapy sent to you on January 29, 2009 and your response to that request sent by you on January 30, 2009. Your response explains most of the discrepancies between the tables provided with the information request. However, it does not explain the difference in the category of hepatic chemoembolization. Please explain how more data in ANP dataset than in A_ANP dataset can result in less number of patients having hepatic chemoembolization based on ANP than that based on A_ANP.

Let me know if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2466 | Silver Spring, MD 20993
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | christy.cottrell@fda.hhs.gov

---

From: sibylle.jennings@novartis.com [mailto:sibylle.jennings@novartis.com]
Sent: Friday, January 30, 2009 2:19 PM
To: Cottrell, Christy L.
Subject: NDA 22-334: Response to Statistical Information Request

Dear Christy,
Please find attached for your upfront information the response to the statistical information request which we received by e-mail yesterday, as well as the cover letter for our submission (seq 30). I will also update the response tracking sheet accordingly and send it by separate e-mail.
Best regards,
Sibylle

Sibylle Jennings
Novartis Pharmaceuticals Corporation
PH, Dev - Oncology DRA II
USEH, Building 104 Room 3K25
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA
Phone: +1 862 7781196
Cell: +1 862 596 4679
Email : sibylle.jennings@novartis.com

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

/s/

Christy Cottrell
2/2/2009 01:53:21 PM
CSO