

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206947Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206947

SUPPL #

HFD # 107

Trade Name LENVIMA

Generic Name Lenvatinib

Applicant Name Eisai, Inc.

Approval Date, If Known 2/13/15

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: Deanne Varney
Title: Senior Regulatory Project Manager
Date: 2/12/15

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

APPEARS THIS WAY ON ORIGINAL



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

/s/

DEANNE R VARNEY
02/12/2015

PATRICIA KEEGAN
02/12/2015

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 206947 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2 PDUFA Goal Date: 4/14/15 Stamp Date: 8/14/2014

Proprietary Name: LENVIMA

Established/Generic Name: lenvatinib

Dosage Form: capsule

Applicant/Sponsor: Eisai, Inc.

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: Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer

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

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

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

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

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

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

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

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

Q3: Does this indication have orphan designation?

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

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

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

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

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

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

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

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

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

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

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

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

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

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

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

Not feasible:

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

***** Not meaningful therapeutic benefit:

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

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

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

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

Δ Formulation failed:

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

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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

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

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

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

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

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

* Other Reason: _____

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

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

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

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

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

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

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

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 ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

Not feasible:

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

***** Not meaningful therapeutic benefit:

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

† Ineffective or unsafe:

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

Δ Formulation failed:

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

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to 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 Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

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

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 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 Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

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

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

* Other Reason: _____

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

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

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

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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

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

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

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

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

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

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

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

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

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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

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

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

If there are additional indications, please 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/

DEANNE R VARNEY
01/14/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 206947 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: LENVIMA Established/Proper Name: Lenvatinib Dosage Form: Capsule		Applicant: Eisai, Inc. Agent for Applicant (if applicable): N/A
RPM: Deanne Varney		Division: DOP2
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> <p>Date of check: _____</p> <p><i>Note: 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.</i></p>
Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is 4/14/2015 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

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

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

Review priority: Standard Priority
 Chemical classification (new NDAs only): NME
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDA: Subpart H	BLA: Subpart E
<input type="checkbox"/> Accelerated approval (21 CFR 314.510)	<input type="checkbox"/> Accelerated approval (21 CFR 601.41)
<input type="checkbox"/> Restricted distribution (21 CFR 314.520)	<input type="checkbox"/> Restricted distribution (21 CFR 601.42)
Subpart I	Subpart H
<input type="checkbox"/> Approval based on animal studies	<input type="checkbox"/> Approval based on animal studies

- | | |
|---|---|
| <input type="checkbox"/> Submitted in response to a PMR | REMS: <input type="checkbox"/> MedGuide |
| <input type="checkbox"/> Submitted in response to a PMC | <input type="checkbox"/> Communication Plan |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU |
| | <input type="checkbox"/> MedGuide w/o REMS |
| | <input type="checkbox"/> REMS not required |

Comments:

❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): Approval 2/13/15 (replacement letter) Approval 2/13/15
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	12/23/2014 (letter) 12/23/2014 (review) 11/20/2014 (letter) 11/18/2014 (review)
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	
• Review(s) (<i>indicate date(s)</i>)	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 10/7/2014 DMEPA: <input type="checkbox"/> None 11/19/2014 DMPP/PLT (DRISK): <input type="checkbox"/> None 12/22/2014 OPDP: <input type="checkbox"/> None 12/31/2014 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None 11/21/2014 (ADL Review) 12/10/2014 (QT IRT Review) 1/9/2015 (Maternal Health)
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	10/7/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan designation, exempt from PREA</u> 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	2/12/2015 2/10/2015 2/5/2015 (2) 2/3/2015 (2) 1/27/2015 1/22/2015 (2) 1/14/2015 1/7/2015 12/23/2014 12/15/2014 12/9/2014 (2) 12/3/2014 12/1/2014 11/25/2014 11/5/2014 11/4/2014 11/3/2014 10/23/2014 10/21/2014 (2) 10/15/2014 10/10/2014 9/2/2014 8/29/2014 (DARRTS 9/3/2014) 8/28/2014 (3)
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	2/3/2015 1/21/2015 1/14/2015 12/17/2014 11/25/2014 (DARRTS 12/23/14) 11/19/2014 11/4/2014 (2) 10/23/2014 10/9/2014 9/25/2014 (DARRTS 10/7/2014) 8/27/2014 (DARRTS 8/28/2014)
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 3/25/2014 (DARRTS 4/15/14)
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 1/12/2011
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 11/25/2014

<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 2/4/2015
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/13/2015
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/12/2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/12/2015 1/20/2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None (2) 1/29/2015 1/26/2015
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	9/23/2014 (filing concurrence) 1/13/2015 (concurrence)
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	1/13/2015 1/12/2015 9/23/2014 (filing)
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	1/7/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 1/14/2015
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 1/27/2015 (letter) 1/20/2015 (2 letters) 1/16/2015 (letter) 1/14/2015 (review)

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None 1/14/2015 9/16/2014 (filing)
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review Concurrence 1/15/2015
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> None 1/14/2015 10/9/2014 (filing)
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>		<input checked="" type="checkbox"/> None requested
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> No separate review 1/14/2015
• Supervisory Review(s) <i>(indicate date for each review)</i>		<input type="checkbox"/> No separate review 1/14/2015
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 2/6/2015 1/13/2015 9/25/2014 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>		<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None <i>2/15/15 - MEMO</i> 1/13/2015 (drug product) 1/13/2015 (drug substance) 1/12/2015 (biopharmaceutics) 9/23/2014 (filing review)
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 11/7/2014 (microbiology) 9/25/2014 (microbiology filing)
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		10/8/2014 (OMPQ filing)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See DP review page 7, 1/13/2015
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: 2/5/2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities

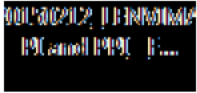
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, February 12, 2015 1:16 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 Labeling Edits

Hi Susan,

As discussed, please find attached additional edits to the lenvatinib labeling. Please review the edits, accept those you agree with, and submit clean and tracked-changes versions to your NDA today if possible. Please confirm receipt and let me know should you have any questions.



Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
02/12/2015

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, February 10, 2015 3:22 PM
To: 'Susan_Mayer@Eisai.com'
Subject: RE: NDA 206947 / Lenvatinib - FDA Edits to Labeling
Attachments: LENVIMA PI and PPI_FDA Edits_20150210.docx

Hi Susan,

Please find attached very minor edits to the PI to correct spacing and formatting issues. Please accept all edits you are in agreement with and submit updated labeling to your NDA by **COB tomorrow, February 11, 2015**. Please submit both clean and tracked-changes versions.

As discussed during the LCM, the carton and container labeling submitted on January 22, 2015, is acceptable.

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

From: Susan_Mayer@Eisai.com [mailto:Susan_Mayer@Eisai.com]
Sent: Friday, February 06, 2015 5:58 PM
To: Varney, Deanne
Subject: RE: NDA 206947 / Lenvatinib - FDA Edits to Labeling

Hi Deanne,

Attached please find our response to the Division's edits to the labeling. As requested, both a clean and tracked-changes version of the revised label are attached. Edits we are in agreement with have been accepted and we have made additional edits in tracked-changes. Lastly, we have reviewed the document for formatting issues, and provided issued/revision dates of 02/2015 where indicated.

We will ensure the formal response is submitted to the NDA by noon Monday, 09 Feb.

Best regards,
Susan

Susan Mayer
Regulatory Core Function Unit
Eisai Product Creation Systems
155 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 201-949-4831
Fax: 201-746-3211
Email: susan_mayer@eisai.com

From: "Varney, Deanne" <Deanne.Varney@fda.hhs.gov>
To: "Susan_Mayer@eisai.com" <Susan_Mayer@eisai.com>
Date: 02/05/2015 12:24 PM

Subject: RE: NDA 206947 / Lenvatin b - FDA Edits to Labeling

Hi Susan,

Please find attached updated versions of the PI and PPI based on discussions during the Late Cycle Meeting yesterday. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit updated labeling to your NDA by **12PM on Monday, February 9th**. Please submit both clean and tracked-changes versions. Please also ensure you review for formatting issues, and provide issued/revision dates of 02/2015 where indicated.

As discussed during the LCM, the carton and container labeling submitted on January 22, 2015, is acceptable.

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

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/s/

DEANNE R VARNEY
02/10/2015

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, February 03, 2015 4:49 PM
To: Susan_Mayer@eisai.com
Subject: NDA 206947 / Lenvatinib - FDA Edits to Labeling

Hello Susan,

Please find attached FDA's second round of labeling edits for the lenvatinib PI and PPI. We will use these versions for discussion during the Late Cycle Meeting tomorrow. There is no need to respond to our edits/comments prior to the 10AM meeting.

Please confirm receipt. See you tomorrow!



LENTAVINIB PI EDOCS
LENTAVINIB PPI EDOCS

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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DEANNE R VARNEY
02/05/2015

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, February 05, 2015 12:24 PM
To: 'Susan_Mayer@eisai.com'
Subject: RE: NDA 206947 / Lenvatinib - FDA Edits to Labeling

Hi Susan,

Please find attached updated versions of the PI and PPI based on discussions during the Late Cycle Meeting yesterday. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit updated labeling to your NDA by **12PM on Monday, February 9th**. Please submit both clean and tracked-changes versions. Please also ensure you review for formatting issues, and provide issued/revision dates of 02/2015 where indicated.

As discussed during the LCM, the carton and container labeling submitted on January 22, 2015, is acceptable.

Please confirm receipt and let me know should you have any questions.



LENVIMA PI FDA Edits_20150203.docx
LENVIMA PPI FDA Edits_20150203.docx

Thank you,
Deanne

From: Varney, Deanne
Sent: Tuesday, February 03, 2015 4:49 PM
To: Susan_Mayer@eisai.com
Subject: NDA 206947 / Lenvatinib - FDA Edits to Labeling

Hello Susan,

Please find attached FDA's second round of labeling edits for the lenvatinib PI and PPI. We will use these versions for discussion during the Late Cycle Meeting tomorrow. There is no need to respond to our edits/comments prior to the 10AM meeting.

Please confirm receipt. See you tomorrow!

<< File: LENVIMA PI_FDA Edits_20150203.docx >> << File: LENVIMA PPI_FDA Edits_20150203.docx >>

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

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DEANNE R VARNEY
02/05/2015

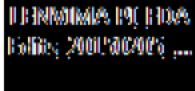
Varney, Deanne

From: Varney, Deanne
Sent: Thursday, February 05, 2015 1:11 PM
To: 'Susan_Mayer@eisai.com'
Subject: RE: NDA 206947 / Lenvatinib - FDA Edits to Labeling

Hi Susan,

We made a few additional edits to the D&A section in Highlights of the PI. Please find the updated version attached. My apologies for the multiple versions.

Please confirm receipt.



Thank you,
Deanne

From: Varney, Deanne
Sent: Thursday, February 05, 2015 12:24 PM
To: 'Susan_Mayer@eisai.com'
Subject: RE: NDA 206947 / Lenvatinib - FDA Edits to Labeling

Hi Susan,

Please find attached updated versions of the PI and PPI based on discussions during the Late Cycle Meeting yesterday. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit updated labeling to your NDA by **12PM on Monday, February 9th**. Please submit both clean and tracked-changes versions. Please also ensure you review for formatting issues, and provide issued/revision dates of 02/2015 where indicated.

As discussed during the LCM, the carton and container labeling submitted on January 22, 2015, is acceptable.

Please confirm receipt and let me know should you have any questions.

<< File: LENVIMA PI_FDA Edits_20150205.docx >> << File: LENVIMA PPI_FDA Edits_20150205.docx >>
Thank you,
Deanne

From: Varney, Deanne
Sent: Tuesday, February 03, 2015 4:49 PM
To: Susan_Mayer@eisai.com
Subject: NDA 206947 / Lenvatinib - FDA Edits to Labeling

Hello Susan,

Please find attached FDA's second round of labeling edits for the lenvatinib PI and PPI. We will use these versions for discussion during the Late Cycle Meeting tomorrow. There is no need to respond to our edits/comments prior to the 10AM meeting.

Please confirm receipt. See you tomorrow!

<< File: LENVIMA PI_FDA Edits_20150203.docx >> << File: LENVIMA PPI_FDA Edits_20150203.docx >>

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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DEANNE R VARNEY
02/05/2015

WRAP UP MEETING MINUTES

February 3, 2015

New NDA 206947
Lenvatinib
Eisai

Submission Date: August 14, 2014
Received Date: August 14, 2014
PDUFA Date: April 14, 2015

Proposed Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Core Review Team:

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Stephanie Aungst, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Gaetan Ladouceur, CMC
Amit Mitra, CMC
Liang Zhou, CMC Team Leader
Ali Al Hakim, CMC (Branch Chief)
Teicher Agosto, CMC (ONDQA RPM)
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader
Robert Schuck, Clinical Pharmacology/Genomics Reviewer
Rosane Charlab Orbach, Clinical Pharmacology/Genomics Team Leader
Okpo Eradiri, Biopharmaceutics Reviewer
Angelica Dorantes, Biopharmaceutics Team Leader
Jessica Cole, Quality Microbiology Reviewer

Consults:

Nick Senior, OPDP / Jessica Cleck Dereneck, OPDP TL
Nathan Caulk, PLT / Barbara Fuller, PLT TL
Afrouz Nayernama, DPV / Tracy Salaam, DPV TL
Carolyn Yancey, DRISK / Naomi Redd, DRISK Acting TL
Otto Townsend, DMEPA / Alice Tu, DMEPA TL
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL
Lauren Iacono-Connors, OSI / Janice Pohlman, OSI TL
Miriam Dinatale, PMHS / Jeanine Best, TL / Alyson Karesh, Acting TL / Vicki Moyer

AGENDA ITEMS:

Reminder of Goal Dates:

Milestone	8 month review
Acknowledgment Letter	August 28, 2014 <i>Issued August 28, 2014</i>
Filing Issues Identified Letter	October 13, 2014 <i>Issued October 10, 2014</i>
Mid-Cycle Meeting	Month 3 – November 12, 2014 <i>Scheduled November 4, 2014</i>
Mid-Cycle Communication	Month 3.5 – November 27, 2014 <i>Scheduled November 19, 2014</i>
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 – January 16, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	Month 5.25 - January 23, 2015
Late Cycle Meeting Target Date	Month 6 if no AC – February 12, 2015 <i>Scheduled February 4, 2015</i>
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 – January 14, 2015 Month 5.1 – January 17, 2015 Month 7 – March 19, 2015 <i>Target: January 30, 2015 (complete)</i> 1.5 weeks pre-action – April 3, 2015 <i>Target: February 12, 2015</i> April 14, 2015 <i>Target: February 13, 2015</i>
Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action – March 10, 2015 <i>Scheduled February 3, 2015</i>
Compile and circulate Action Letter and Action Package	3 weeks pre-action – March 24, 2015 <i>Circulating</i>
FINAL Action Letter Due	April 14, 2015 <i>Target: February 13, 2015</i>

Discussion: FDA will discuss the Drug Snapshot Website with Eisai at the Late Cycle Meeting. RPM will provide Eisai with the tables that need to be completed and request a response by February 11, 2015. Team will confirm that OMPQ will attend the LCM.

Discuss Remaining Outstanding Pre-Action Items:

1. **Target Action Date:** **Friday, February 13, 2015**
2. **Labeling:**

- Counter-proposal received January 22, 2015. Currently under review and will discuss at the late-cycle meeting on February 4, 2015.
- **Discussion:** CDTL requested that if any disciplines agree to any of Eisai's proposed changes to the label, the discipline should provide an addendum to their review explaining what Eisai-proposed changes were accepted and why.

3. Signed Review Status:

- a. Primary Reviews: Complete
- b. Secondary Reviews: Complete
- c. Consult Reviews: Complete
- d. CDTL: Complete
- e. Division Director: Pending
- f. Office Director: Pending

4. PMCs and PMRs: One CMC PMC and one clinical PMR, both agreed to by Eisai and both development templates are signed-off in DARRTS.

5. Postmarket Safety Surveillance: What adverse events should DPV look for once lenvatinib is on the market?

Discussion: There are no specific adverse events to monitor for.

6. Press Release/ASCO Burst/Information Advisory: PR and IA have been reviewed by DOP2. The team will draft the Burst after the next round of labeling.

7. Approval Letter: Circulating

8. Inspections:

- a. **Clinical Site Inspections:** Complete. No issues.
- b. **Manufacturing Site Inspections:** Patheon-Burlington DP manufacturing site inspected week of January 26, 2015. Update pending.

Discussion: ONDQA will follow-up with OMPQ regarding inspection status. The team will also ask Eisai at the LCM if a 483 was issued, and if one was issued will request Eisai provide a copy to DOP2.

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/s/

DEANNE R VARNEY
02/03/2015



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

Memorandum

Date: February 3, 2015
From: Deanne Varney, RPM, DOP2/OHOP/CDER/FDA
Subject: Request for Information Intended to Populate the FDA Drug Trials Snapshot Website for NDA 206947 (lenvatinib)

Dear Ms. Mayer:

We are requesting your assistance in populating the attached tables for your New Molecular Entity, lenvatinib, which is currently under review in the Division. This information will be posted publicly, if your application is approved, at the FDA drug snapshot website:
<http://www.fda.gov/Drugs/InformationOnDrugs/ucm412998.htm>.

We are asking for this information to allow for greater transparency by providing information to the public about participation in clinical trials for newly-approved drugs and biologics.

The website will include information on the study design, the results of efficacy and safety studies, and whether there were any differences in efficacy and side effects among sex, race, and age subgroups. It is not intended to replace or replicate the package insert, which are intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- Information that focus on subgroup data and analyses
- Links to PI for the product and to the FDA reviews at Drugs@FDA
- Information will be published approximately 30 days after drug/biologic approval

Therefore, we are requesting that you provide your data and complete the attached tables. If these data differ or are not contained in the NDA please provide descriptions of the analyses used to generate the data and any programs used to generate or analyze the data.

We are requesting you submit this information no later than February 11, 2015. Please provide a courtesy copy to me via email as well.

Thank you in advance for your cooperation.

If you have any questions, please call me at 301-796-0297.

Sincerely,

{See appended electronic signature page}

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

PROPOSED SHELL TABLES

Table 1. Listing of Clinical Trials for the Efficacy Analysis

Study ID	No. of patients enrolled in the Drug X Arm	No. of patients enrolled in the Comparator Arm

Table 2.1 Baseline Demographics, Single or Pooled Pivotal Efficacy Trials

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 2.2 Baseline Demographics, Multiple Pivotal Efficacy Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 3 Subgroup Analysis of Primary Endpoint, Pivotal Efficacy Trials

Demographic Subgroup	Trial #1 (N=)			Trial #2 (N=)		
	Comparator/control (n=) n (%)	Treatment arm (n=) n (%)	Difference (95% CI)	Comparator/control (n=) n (%)	Treatment arm (n=) n (%)	Difference (95% CI)
Overall Response/All patients						
Sex						
Male						
Female						
Age Group						
<17 years						
≥17 - <65 years						
≥65 years						
≥75 years						
Race						
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						
Hispanic or Latino						
Not Hispanic or Latino						
Region						
United States						
Rest of the World						
Canada						
South America						
Europe						
Asia						
Africa						

Source: list datasets or other sources of information

Table 4 Safety Population, Size and Denominators

Safety Database for the Study Drug ¹ Individuals exposed to the study drug in this development program for the indication under review N= (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=)	Active Control (n=)	Placebo (n=)
Normal Volunteers			
Controlled trials conducted for this indication ²			
All other than controlled trials conducted for this indication ³			
Controlled trials conducted for other indications ⁴			

¹ *study drug* means the drug being considered for approval; do not include comparator arm drugs, placebo, or vehicle control in this table

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

**Table 5.1 Baseline Demographics, Safety Population, Single or Pooled Trials
(If efficacy population = safety population, refer to Table 2.1 or 2.2)**

Demographic Parameters	Comparator/ Control (n=) n (%)	Treatment Group(s) (n=)		Total (n=) n (%)
		Treatment arm #1 (n=) n (%)	Treatment arm #2 (n=) n (%)	
Sex				
Male				
Female				
Age				
Mean years (SD)				
Median (years)				
Min, max (years)				
Age Group				
<17 years				
≥17 - <65 years				
≥65 years				
≥75 years				
Race				
White				
Black or African American				
Asian				
American Indian or Alaska Native				
Native Hawaiian or Other Pacific Islander				
Other				
Ethnicity				
Hispanic or Latino				
Not Hispanic or Latino				
Region				
United States				
Rest of the World				
Canada				
South America				
Europe				
Asia				
Africa				

Source: list datasets or other sources of information

Table 5.2 Baseline Demographics, Safety Population, Multiple Trials

Demographic Parameters	Trial #1 (N=)		Trial #2 (N=)		Total (n=) n (%)
	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	Comparator/ Control (n=) n (%)	Treatment arm (n=) n (%)	
Sex					
Male					
Female					
Age					
Mean years (SD)					
Median (years)					
Min, max (years)					
Age Group					
<17 years					
≥17 - <65 years					
≥65 years					
≥75 years					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Ethnicity					
Hispanic or Latino					
Not Hispanic or Latino					
Region					
United States					
Rest of the World					
Canada					
South America					
Europe					
Asia					
Africa					

Source: list datasets or other sources of information

Table 6.1 Subgroup Analysis of TEAEs, Safety Population

Demographic Subgroup	Comparator/Control		Treatment		Relative Risk	95% CI	
	n (%)	Total, N	n (%)	Total, N		LL	UL
Any TEAEs							
Sex							
Male							
Female							
Age Group							
<17 years							
≥17 - <65 years							
≥65 years							
≥75 years							
Race							
White							
Black or African American							
Asian							
American Indian or Alaska Native							
Native Hawaiian or Other Pacific Islander							
Other							
Ethnicity							
Hispanic or Latino							
Not Hispanic or Latino							
Region							
United States							
Rest of the World							
Canada							
South America							
Europe							
Asia							
Africa							

Source: list datasets or other sources of information

**Table 6.2 Subgroup Analysis by Sex of Common AEs, Safety Population
(Events ≥ 2% of drug-treated subjects and more frequent than placebo)¹**

MedDRA System Organ Class Preferred Term	Male (N=)		Female (N=)	
	Comparat or/Contro I (n=) n (%)	Total Drug X (n=) n (%)	Comparat or/Contro I (n=) n (%)	Total Drug X (n=) n (%)
Gastrointestinal disorders				
Nausea				
Vomiting				
Diarrhea				
Abdominal pain				
General disorders/administration site conditions				
Fatigue				
Edema peripheral				
Infections and Infestations				
Influenza				
Urinary tract infection				
Injury, poisoning and procedural complications				
Fall				
Contusion				
Investigations				
Weight increased				
Blood CPK increased				
Musculoskeletal & connective tissue disorders				
Arthralgia				
Nervous system disorders				
Dizziness				
Headache				
Psychiatric disorders				
Depression				
Insomnia				
Respiratory, thoracic & mediastinal disorders				
Cough				
Skin & subcutaneous tissue disorders				
Rash				
Pruritus				

Source: list datasets or other sources of information

Example of an application-specific adverse event

Table 6.3 Subgroup Analysis by Age of Dizziness/Gait Disturbance Adverse Events, Safety Population*

MedDRA Preferred Term	Age ≥17-<65 years (N=)		Age ≥65 years (N=)	
	Comparat or/Control (n=) n (%)	Total Drug X (n=) n (%)	Comparat or/Control (n=) n (%)	Total Drug X (n=) n (%)
Dizziness				
Ataxia				
Vertigo				
Balance disorder				
Gait disturbance				
Coordination abnormal				
Cerebellar syndrome				
Cerebellar ataxia				
Vestibular ataxia				
Vestibular disorder				
Total				

*Pediatric subjects were not included in the safety population
Source: list datasets or other sources of information

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/s/

DEANNE R VARNEY
02/03/2015

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, January 27, 2015 1:49 PM
To: 'Susan_Mayer@Eisai.com'
Subject: RE: NDC Numbers - Lenvatinib

Hi Susan,

I have consulted with the necessary groups across FDA, and have determined that your below proposal regarding NDC numbers is acceptable. Additionally, I have been informed that a manual override will not be necessary. The manual override your SPL vendor referred to is an override of the automated validations which will reject a submission if any of the data validation rules are violated. FDA sometimes allow an override of the validations if a listing submission changes certain information already associated with an NDC (like a proprietary name or formulation) in order to correct a mistake. However, there should not be any pre-existing listing records for this product that would interfere with the submission as described below.

Please let me know if you have any additional questions, and thank you for your patience.

Deanne

From: Susan_Mayer@Eisai.com [mailto:Susan_Mayer@Eisai.com]
Sent: Tuesday, January 20, 2015 9:29 AM
To: Varney, Deanne
Subject: NDC Numbers - Lenvatinib

Dear Deanne,

While addressing labeling comments received on 14 January, in particular Comment #44 contained within the USPI:

- the commercial package size (last two digits) should be differentiated between the 5-day blister card and the 30-day carton labeling
- recommendation to avoid (b) (4) As currently presented, (b) (4) is not an effective differentiating feature.

Eisai would like to propose the following NDC #s

Product Strength 5-day blister card 30-day carton label

10 mg	62856-710-05	62856-710-30
14 mg	62856-714-05	62856-714-30
20 mg	62856-720-05	62856-720-30
24 mg	62856-724-05	62856-724-30

Because the 10 mg and 20 mg product strengths are created using the 10 mg capsule, they would ordinarily be assigned the same 3-digit product code in SPL. In order to avoid confusion between these 2 product strengths, we propose assigning numerically different 3 digit product codes to the 10 and 20 mg strength. We have been informed by our SPL vendor that in order to allow the above NDC's, a manual override will need to be permitted to avoid failing validation.

Eisai request confirmation that the above proposal is acceptable and a manual override will be permitted.

Thanks very much for your help.

Best regards,
Susan

Susan Mayer
Regulatory Core Function Unit
Eisai Product Creation Systems
155 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 201-949-4831
Fax: 201-746-3211
Email: susan_mayer@eisai.com

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/s/

DEANNE R VARNEY
01/27/2015

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, January 22, 2015 8:39 PM
To: Susan_Mayer@eisai.com
Subject: NDA 206047 / Lenvatinib --- Information Request

Hi Susan,

Please provide the study numbers and NDA location of the reversibility studies noted in Eisai's comment number 20 in the PI. Please also submit this information as an amendment to your NDA.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
01/22/2015

TEAM MEETING MINUTES

January 21, 2015

New NDA 206947
Lenvatinib
Eisai

Submission Date: August 14, 2014
Received Date: August 14, 2014
PDUFA Date: April 14, 2015

Proposed Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Core Review Team:

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Stephanie Aungst, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Gaetan Ladouceur, CMC
Amit Mitra, CMC
Liang Zhou, CMC Team Leader
Ali Al Hakim, CMC (Branch Chief)
Teicher Agosto, CMC (ONDQA RPM)
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader
Robert Schuck, Clinical Pharmacology/Genomics Reviewer
Rosane Charlab Orbach, Clinical Pharmacology/Genomics Team Leader
Okpo Eradiri, Biopharmaceutics Reviewer
Angelica Dorantes, Biopharmaceutics Team Leader
Jessica Cole, Quality Microbiology Reviewer

Consults:

Nick Senior, OPDP / Jessica Cleck Dereneck, OPDP TL
Nathan Caulk, PLT / Barbara Fuller, PLT TL
Afrouz Nayernama, DPV / Tracy Salaam, DPV TL
Carolyn Yancey, DRISK / Naomi Redd, DRISK Acting TL
Otto Townsend, DMEPA / Alice Tu, DMEPA TL
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL
Lauren Iacono-Connors, OSI / Janice Pohlman, OSI TL
Miriam Dinatale, PMHS / Jeanine Best, TL / Alyson Karesh, Acting TL / Vicki Moyer

AGENDA ITEMS:

1. Review Status:

- Priority Review (PDUFA V --- 8 month review)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of lenvatinib has been conducted under INDs (b) (4) and 113656

2. Reminder of Milestone Dates for 8-Month Priority Review Clock:

Milestone	8 month review
Acknowledgment Letter	August 28, 2014 <i>Issued August 28, 2014</i>
Filing Issues Identified Letter	October 13, 2014 <i>Issued October 10, 2014</i>
Mid-Cycle Meeting	Month 3 – November 12, 2014 <i>Scheduled November 4, 2014</i>
Mid-Cycle Communication	Month 3.5 – November 27, 2014 <i>Scheduled November 19, 2014</i>
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 – January 16, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	Month 5.25 - January 23, 2015
Late Cycle Meeting Target Date	Month 6 if no AC – February 12, 2015 <i>Scheduled February 4, 2015</i>
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 – January 14, 2015 Month 5.1 – January 17, 2015 Month 7 – March 19, 2015 <i>Target: January 30, 2015 (complete)</i> 1.5 weeks pre-action – April 3, 2015 <i>Target: February 13, 2015</i> April 14, 2015 <i>Target: February 14, 2015</i>
Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action – March 10, 2015 <i>Scheduled February 3, 2015</i>
Compile and circulate Action Letter and Action Package	3 weeks pre-action – March 24, 2015 <i>Target: January 26, 2015</i>
FINAL Action Letter Due	April 14, 2015 <i>Target: February 14, 2015</i>

Discussion: The team will target a February 14, 2015 action, but this will be contingent on the results of the manufacturing facilities inspections.

3. **Reminder:** Late Cycle Meeting briefing package due to Eisai January 23, 2015.

- Draft is circulating with edits due COB today.
- Discussion: FDA will inform Eisai that there are no major issues to discuss and give them the option for a teleconference instead of a face-to-face meeting.

4. **Reminder:** PMR/PMC templates need to be signed-off in DARRTS prior to the action.

5. **Review Issues:**

- Clinical:** Review complete.
- Statistics:** Review complete.
- Clinical Pharmacology:** Review complete.
- Pharmacometrics:** Review complete.
- Genomics:** Review complete.
- Nonclinical:** Review complete.
- CMC:** Review complete.
- Biopharmaceutics:** Review complete.
- Microbiology:** Review complete.

6. **Inspections:**

a. **Clinical Site Inspections:**

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
CRO: (b) (4)	October 9 th -16 th , 2014	Completed	NAI. No major issues.	N/A
Dr. Shah (Ohio)	October 6-17, 2014	Completed	VAI. No major issues.	1018
Dr. Francoise Bonichon (Bordeaus France)	December 1-5, 2014	Completed	VAI	1401
Dr. Christelle	November 17-21,	Completed	VAI	1402

Fouchardiere (Lyon France)	2014			
Dr. Hiroto Ishiki (Chiba Japan)	December 1-5 2014	Completed	VAI	1201
Dr. Eun Lee (S. Korea)	December 8-12, 2014	Completed	VAI	3001

b. Manufacturing Site Inspections:

Establishment Name	EER Creation Date	Country Code	Responsibilities	Profile Code	PAI Status	Anticipated Inspection Dates	Compliance Status
(b) (4)	09.22/2014	USA	Packaging	CHG	Acceptable- Based on Profile	N/A	AC
PATHEION INC. TORONTO REGION OPERATIONS	09.22/2014	CAN	Drug Product Manufacturing and Testing	CHG	Pending	January 2015	PN
EISAI COMPANY, LTD.	09.22/2014	JPN	Drug Substance Manufacturing and Testing	(b) (4)	Pending	November 2014	PN
EISAI INC	09.22/2014	USA	Drug Product Testing	CTL	Pending	Under evaluation by District	PN
PATHEON INC.- BURLINGTON CENTURY OPERATIONS	09.22/2014	CAN	Drug Product Testing	CTL	Pending	January 2015	PN

7. Upcoming Meetings:

- **Labeling Meetings:**

- a. ~~December 1, 2014: Clinical and Statistics Sections 1, 14~~
- b. ~~December 2, 2014: Clin Pharm and Clinical Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3~~
- c. ~~December 8, 2014: Clinical, CMC, DMEPA Sections 3, 11, 16~~
- d. ~~December 10, 2014: Clinical Sections 4, 5, 6, 17~~

e. ~~December 11, 2014: Clinical, Nonclinical, Maternal Health—
Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13~~

f. ~~January 12, 2015: Review of consult edits / final review~~

g. February 3, 2015: Review of Eisai counter-proposal

- **Monthly Team Meetings:**

- a. ~~October 23, 2014~~

- b. ~~November 19, 2014~~

- c. ~~December 17, 2014~~

- d. ~~January 21, 2015~~

- e. February 16, 2015

- f. March 19, 2015

- g. April 6, 2015

- **Late Cycle Meeting:** February 4, 2015

- **Wrap- Up Meeting:** February 3, 2015

8. **ODAC:** Not Required

9. **SGE's:** The team decided not to pursue SGE consults for this application.

8. **Additional Items or Issues:**

- Team will draft ASCO burst once labeling is received back from Eisai
- Team will follow-up with OMA regarding status of press release and possible mid-February action

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/s/

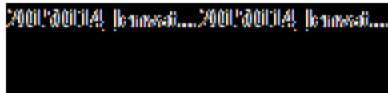
DEANNE R VARNEY
01/21/2015

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, January 14, 2015 11:13 AM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 - Proposed Labeling

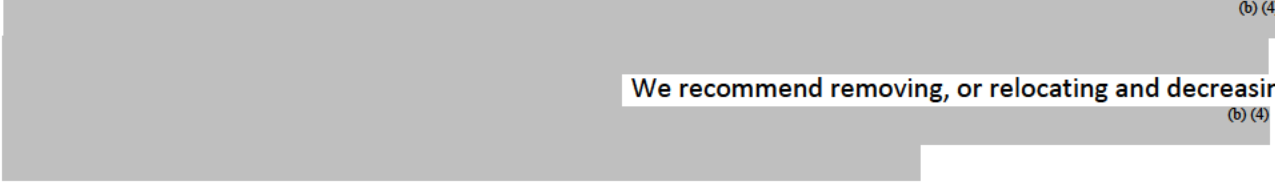



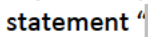


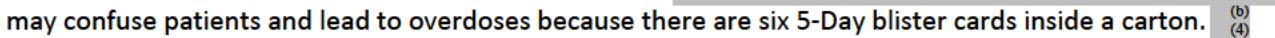
Hello Susan,

Please find attached our proposed edits to the lenvatinib PI and PPI. In addition to these edits, please update all table and figure numbers as needed and correct formatting where required.



We also have the following comments on your carton and container labeling:

Container Labels (5-Day blister card):

1. Revise the presentation of the proprietary name so only the first letter in the proprietary name is capitalized. Words written in all-capital letters are less legible than words written in mixed case letters.
2.  (b) (4)
We recommend removing, or relocating and decreasing the (b) (4)
3. Replace the statement  (b) (4) with the statement "Each 5-day card contains:  (b) (4) ". Additionally, as currently presented, the statement competes in prominence with and is too close in proximity to the daily dosage statement. We recommend decreasing the font size and relocating the statement " (b) (4)". For example, relocate the statement  (b) (4) on the PDP to the lower right or lower left corner.
4. Each of the proposed 5-Day Blister Card labels contains  (b) (4) This may confuse patients and lead to overdoses because there are six 5-Day blister cards inside a carton.  (b) (4) To provide clearer instructions to patients, we recommend that you label the blister cards as follows:



5. Ensure that the capsule images on the container labels represent the actual capsules and reflect the true, size, color, and imprint of the approved lenvatinib 4 mg and 10 mg capsules.

Carton Labeling:

6. The statement “30-Day Supply” competes in prominence with and is too close in proximity to the daily dosage statement. We recommend decreasing the font size of the statement “30-Day Supply” on the PDP and back panel, and relocating the statement to the lower right corner on the side panel. To create more space on the PDP, consider relocating the manufacturer and distributor information to the right side panel (same panel that contains the lot number and expiry information).

7. For consistency with Section 16: How Supplied/Storage and Handling of the PI and to provide clarity, revise the “^{(b) (4)}” contents statement on the PDP to read “XX mg daily-dose carton containing 6 cards ^{(b) (4)}”. The use of the ^{(b) (4)} is redundant and unnecessary.

Please review our proposed edits and comments to the lenvatinib labeling. Please accept all edits you are in agreement with, make any additional edits in tracked-changes, and submit your counterproposal along with any supporting data to your NDA by **Friday, January 23, 2015**, with a courtesy copy to me via email.

Please confirm receipt of this communication and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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

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/s/

DEANNE R VARNEY
01/14/2015

Agosto, Teicher

From: Agosto, Teicher
Sent: Monday, January 12, 2015 12:20 PM
To: Susan_Mayer@eisai.com; Monica_Lee@Eisai.com
Cc: Varney, Deanne
Subject: Information Request NDA 206947

Dear Susan ,

We are requesting a written commitment concerning your New Drug Application- NDA 206947. We request a prompt response to this request no later than COB today, January 12, 2015.

Commit to submitting a prior approval supplement with a request to sunset the test and acceptance criterion based on the submitted data with the following information:

1. A limit test for leve [REDACTED] ^{(b) (4)} of the drug substance in the drug product including the analytical method and its validation.
2. Supporting data for the limits.
3. Dates and milestones for completion of the above tasks.

In addition to formally submitting this information, please send me a courtesy copy via email.

Please confirm receipt of this written commitment.

Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

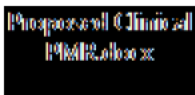
Teicher Agosto, Pharm D, RPh
Regulatory Health Project Manager
FDA\CDER\OPS
Office of New Drug Quality Assessment
10903 New Hampshire Ave W021,Rm 2615
Silver Spring, MD 20993
Teicher.agosto@fda.hhs.gov
P: (240) 402-3777

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, January 07, 2015 12:55 PM
To: Susan_Mayer@eisai.com
Subject: NDA 206947 / Lenvatinib --- Proposed Clinical PMR

Hello Susan,

Please find attached a proposed clinical post-marketing requirement (PMR) that the FDA review team has determined is necessary. Please note that additional PMRs/PMCs could be forthcoming.



Please review the attached PMR and propose dates for each of the four milestones that are outlined. Please note that missing goal dates will require you to provide justification for the delays, and such delays could result in enforcement actions. Therefore, you should provide some buffer time for unexpected difficulties in completing the scheduled milestones, and use due diligence in proposing the schedule taking into account time for recruitment of study institutions, IRB approvals, accrual rate, drop-out rate, etc.

Please submit this PMR and your proposed milestone dates as a formal amendment to your NDA. **Please confirm receipt** and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

Proposed Post-Marketing Requirement:

1. Conduct a clinical trial to evaluate whether an oral starting dose of 20 mg or 14 mg daily will provide comparable efficacy to a 24 mg starting Dose, but have a better safety profile. Safety assessments will include evaluations for \geq Grade 3 adverse reactions, all adverse reactions, and serious adverse reactions.

Proposed PMR Milestone Dates:

Submit Draft Protocol (3 months before final protocol submission): MM/YY

Final Protocol Submission: MM/YY

Trial Completion: MM/YY

Final Clinical Trial Report Submission: MM/YY

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/s/

DEANNE R VARNEY
01/07/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206947

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Eisai, Inc.
155 Tice Boulevard
Woodcliff Lake, NJ 07677

ATTENTION: Susan Mayer
Director, Global Regulatory Affairs

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) dated August 14, 2014, received August 14, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lenvatinib Capsules, 4 mg and 10 mg.

We also refer to your December 5, 2014, correspondence, received December 5, 2014, requesting reconsideration of your proposed proprietary name, Lenvima.

We have completed our review of the information submitted in support of your Request for Reconsideration of the proposed proprietary name, Lenvima, as well as our previous evaluations of your proposed name. Based on the information we have reviewed, we conclude that there appears to be minimal risk of confusion between Lenvima and Levemir. Therefore, we conclude that your proposed proprietary name, Lenvima is acceptable.

If any of the proposed product characteristics as stated in your December 5, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Deanne Varney, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
12/23/2014

MEMORANDUM of TELECONFERENCE

MEETING DATE: November 25, 2014
TIME: 1:00 PM EST
LOCATION: WO/Bld. 22. Rm. 5313
APPLICATION: NDA 206947
DRUG NAME: Lenvatinib
TYPE OF MEETING: Teleconference

MEETING CHAIRS: Kellie Taylor, Deputy Director, Office of Medication Error Prevention and Risk Management
Lubna Merchant, Associate Director, Division of Medication Error Prevention and Analysis

MEETING RECORDER: Frances Fahnbulleh, OSE SRPM

FDA ATTENDEES:

Kellie Taylor – Deputy Director, Office of Medication Error Prevention and Risk Management
Lubna Merchant – Associate Director, Division of Medication Error Prevention and Analysis
Otto Townsend – Safety Evaluator, Division of Medication Error Prevention and Analysis
Alice (Chi-Ming) Tu- Team Lead, Division of Medication Error Prevention and Analysis
Frances Fahnbulleh- Safety Regulatory Health Project Manager, Office of Surveillance and Epidemiology
Joseph Gootenberg- Deputy Director, Division of Oncology Products 2
Abhilasha Nair- Medical Officer, Division of Oncology Products 2
Deanne Varney- Regulatory Health Project Manager, Division of Oncology Products 2
Virginia Behr- CDER Ombudsman

EISAI INC. ATTENDEES:

John Collins, Senior Director, Oncology Marketing
Corina Dutcus, Executive Director, Clinical Research, Oncology
Alton Kremer, Deputy President, Oncology
Susan Mayer, Director, Global Regulatory Affairs, Oncology
Alexis Reisin Miller, Senior Director, Global Regulatory Policy and Intelligence
Ginny Beakes-Read, Executive Director, Global Regulatory Policy and Intelligence
Martina Struck, President, Global Regulatory Affairs
Dimitris Voliotis, VP Clinical Research, Oncology

BACKGROUND:

The division of Medication Error Prevention and Analysis (DMEPA) issued a letter to Esai, Inc. on November 20, 2014, informing them that the proposed proprietary name “Lenvima” had been found unacceptable. DMEPA explained in the letter, that a collective analysis of the name similarity, post-marketing experience with other reported errors, and the prescription simulation

study misinterpretation led to the conclusion that the name “Lenvima” is vulnerable to confusion with Levemir, a drug currently marketed for the treatment of diabetes mellitus. Upon receipt of the letter, Eisai requested a teleconference with DMEPA to further discuss the issue. Eisai provided a document which contained background information as well as a list of questions that would serve as the basis for discussion.

MEETING OBJECTIVES:

The purpose of the teleconference was to have a discussion with the sponsor regarding sponsor’s questions related to the denial of the proposed name, Lenvima and discuss a path forward for Eisai to secure a proprietary name for their product.

DISCUSSION (if any)

Eisai began by noting that they do not want to delay product launch due the unacceptability of the proposed proprietary name. They went on to clarify that the information they had previously provided regarding distribution and administration of Lenvima (Section 1.3) was incorrect. They had stated the following: INFORMATION ABOUT PRODUCT DISPENSING AND DELIVERY, in particular Item 1, Likely Care Environments for Dispensing and Use: “The proposed distribution of Lenvima is through the retail and/or hospital pharmacy setting.”

They clarified that lenvatinib will not be distributed to hospitals unless through a specialty pharmacy or 340B institution. They emphasized that Lenvima will be distributed exclusively through two Specialty Pharmacies (Accredo and Biologics), as well as, potentially, 340B health care facilities, and that all requests for lenvatinib will go through the oncology groups in those pharmacies; therefore, the exclusive distribution of Lenvima through specialty pharmacies, dramatically reduces the likelihood that any patient prescribed **Lenvima** would get **Levemir**.

DMEPA responded noting that the lack of an approved proprietary name would not affect Eisai’s ability to market this product if the application is approved. A proprietary name is not required by the agency at the time of approval and Eisai can market the product under the established name.

DMEPA also stated that we have preliminarily considered the specialty pharmacy distribution, and that our experience with drugs being dispensed by specialty pharmacies has been mixed. DMEPA noted that the information regarding the specialty pharmacies could be considered as part of a request for reconsideration or if an alternate name were to be proposed. DMEPA also pointed out that the specialty pharmacy distribution addresses the risk of confusion in only one direction (i.e. patient receiving Lenvima by mistake) but does not address the potential risk of confusion that could occur when patients are admitted to a hospital and an order of Lenvima is misinterpreted as Levemir and patient received Levemir. DMEPA advised that Eisai address the risk of confusion in both directions (i.e. misinterpretation of Lenvima as Levemir, and vice versa).

Eisai also inquired about the sample size used for the simulation studies and if FDA considered that the first study did not identify any misinterpretations and if that was taken into

consideration. DMEPA responded that the first study had 92 respondents, and the second study had 95 respondents. DMEPA also discussed the limitations of the Simulation studies, and our approach to interpreting findings from such studies into our overall risk assessment of a proposed proprietary name.

DMEPA identified two pathways forward if Eisai desired to pursue a proprietary name for the product: a request for reconsideration, or submission of an alternate proposed proprietary name. If Eisai submits a request for reconsideration, DMEPA encouraged Eisai to address the concerns that were outlined in the letter finding Lenvima unacceptable, and the concerns discussed in this teleconference. Eisai was encouraged to include all relevant information in their proprietary name submission.

Eisai asked if DMEPA would review an alternate name in less than the typical 90 days. DMEPA stated that they would work with OND colleagues and make an effort to review expeditiously in alignment with any anticipated action dates.

Eisai stated that they will submit a request for reconsideration and inquired as to what the timeline is for the reconsideration process. DMEPA stated that the timeline for reconsideration is also a 90 day clock, and that we would make an effort to review expeditiously in alignment with any anticipated action dates.

ACTION ITEMS

Eisai agreed to take FDA's recommendations under advisement and would inform us on how they plan to proceed.

The Teleconference ended at approximately 1:35PM EST

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/s/

LUBNA A MERCHANT
12/23/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, December 23, 2014 10:32 AM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 - Clinical IR

Hello Susan,

Please provide the following information for clinical studies 201,208 and 303 as soon as possible:

1. Total number of investigators and subinvestigators identified in each study (only state number for each, we already have the list).
2. Number of investigators and subinvestigators who are sponsor employees (including both full-time and part-time employees) in each of the three studies.

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/23/2014

TEAM MEETING MINUTES

December 17, 2014

New NDA 206947
Lenvatinib
Eisai

Submission Date: August 14, 2014
Received Date: August 14, 2014
PDUFA Date: April 14, 2015

Proposed Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Core Review Team:

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Stephanie Aungst, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Gaetan Ladouceur, CMC
Amit Mitra, CMC
Liang Zhou, CMC Team Leader
Ali Al Hakim, CMC (Branch Chief)
Teicher Agosto, CMC (ONDQA RPM)
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader
Robert Schuck, Clinical Pharmacology/Genomics Reviewer
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Okpo Eradiri, Biopharmaceutics Reviewer
Angelica Dorantes, Biopharmaceutics Team Leader
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Miriam Dinatale, PMHS / Jeanine Best, TL / Alyson Karesh, Acting TL / Vicki Moyer

AGENDA ITEMS:

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- Priority Review (PDUFA V --- 8 month review)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of lenvatinib has been conducted under INDs (b) (4) and 113656

2. Reminder of Milestone Dates for 8-Month Priority Review Clock:

Milestone	8 month review
Acknowledgment Letter	August 28, 2014 <i>Issued August 28, 2014</i>
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Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action – March 10, 2015 <i>Scheduled February 3, 2015</i>
Compile and circulate Action Letter and Action Package	3 weeks pre-action – March 24, 2015
FINAL Action Letter Due	April 14, 2015

Discussion: The CMC team noted that there are potential CMC PMCs. The clinical team will have one PMR to evaluate whether a lower dose of lenvatinib will result in an improved safety profile. The other disciplines do not have any

proposed PMCs/PMRs. The relevant disciplines will begin drafting the PMC/PMR development templates and CMC will begin discussing their proposed PMCs with Eisai.

3. **Reminder:** Discipline review letter(s) are due January 16, 2015. Which disciplines anticipate having issues for inclusion in a DR letter? If multiple disciplines, should we consider issuing a combined DR letter?

Discussion: No disciplines have issues for inclusion in a DR letter.

4. **Reminder:** Late Cycle Meeting briefing package due to Eisai January 23, 2015.

The package should consist of:

- Meeting agenda
- List of attendees
- A current assessment of the need for REMS or other risk management actions (if not already determined)
- A brief memorandum from the review team outlining:
 - Dates of any DR letters issued to date. The memorandum should not duplicate the information from the DR letters
 - Substantive application issues not included in a DR letter. If there are no substantive issues for a discipline, a statement to that effect should be included.

5. Request update from DMEPA on Eisai's request for reconsideration of the proprietary name LENVIMA

Discussion: The DMEPA reviewer determined that Eisai addressed the outpatient issue but didn't address in-patient hospitalization. The request is with DMEPA upper-management and will most likely be denied. DMEPA hopes to complete their review by mid-January.

6. **Review Issues:**

- a. **Clinical:** No issues.
- b. **Statistics:** No issues.
- c. **Clinical Pharmacology:** No issues.
- d. **Pharmacometrics:** No issues.
- e. **Genomics:** No issues.
- f. **Nonclinical:** No issues.

- g. **CMC:** Potential PMCs.
 - h. **Biopharmaceutics:** No updates at this time.
 - i. **Microbiology:** Review is complete with no outstanding issues.
 - j. **Regulatory:** No issues.
7. **Inspections:**
- a. **Clinical Site Inspections:**

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
CRO: (b) (4)	October 9 th -16 th , 2014	Completed	NAI. No major issues.	N/A
Dr. Shah (Ohio)	October 6-17, 2014	Completed	VAI. No major issues.	1018
Dr. Françoise Bonichon (Bordeaux France)	December 1-5, 2014	Scheduled	VAI	1401
Dr. Christelle Fouchardiere (Lyon France)	November 17-21, 2014	Scheduled	VAI	1402
Dr. Hiroto Ishiki (Chiba Japan)	December 1-5 2014	Scheduled	VAI	1201
Dr. Eun Lee (S. Korea)	December 8-12, 2014	Scheduled	VAI	3001

Discussion: OSI is reviewing all preliminary findings and will discuss with the clinical team to confirm if issues suggest considering censoring of specific subjects.

b. **Manufacturing Site Inspections:**

Establishment Name	EER Creation Date	Country Code	Responsibilities	Profile Code	PAI Status	Anticipated Inspection Dates	Compliance Status
(b) (4)	09.22/2014	USA	Packaging	CHG	Acceptable-Based on Profile	N/A	AC
PATHEION INC. TORONTO REGION OPERATIONS	09.22/2014	CAN	Drug Product Manufacturing and Testing	CHG	Pending	January 2015	PN

EISAI COMPANY, LTD.	09.22/2014	JPN	Drug Substance Manufacturing and Testing	(b) (4)	Pending	November 2014	PN
EISAI INC	09.22/2014	USA	Drug Product Testing	CTL	Pending	Under evaluation by District	PN
PATHEON INC.- BURLINGTON CENTURY OPERATIONS	09.22/2014	CAN	Drug Product Testing	CTL	Pending	January 2015	PN

Discussion: Pending. RPM will confirm dates of January inspections with OMPQ.

8. Upcoming Meetings:

- **Labeling Meetings:**

- a. ~~December 1, 2014: Clinical and Statistics Sections 1, 14~~
- b. ~~December 2, 2014: Clin Pharm and Clinical Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3~~
- c. ~~December 8, 2014: Clinical, CMC, DMEPA Sections 3, 11, 16~~
- d. ~~December 10, 2014: Clinical Sections 4, 5, 6, 17~~
- e. ~~December 11, 2014: Clinical, Nonclinical, Maternal Health Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13~~
- f. January 12, 2015: Review of consult edits / final review

- **Monthly Team Meetings:**

- a. ~~October 23, 2014~~
- b. ~~November 19, 2014~~
- c. ~~December 17, 2014~~
- d. January 21, 2015
- e. February 16, 2015
- f. March 19, 2015
- g. April 6, 2015

- **Late Cycle Meeting:** February 4, 2015 / Pre-LCM internal meeting January 20, 2015. *Note: LCM briefing package due to Eisai Friday, January 23rd.*
- **Wrap- Up Meeting:** February 3, 2015.

Discussion:

9. **ODAC: Not Required**

10. **SGE's:** The proposed SGE's and patient representative listed below have agreed to participate. The Competing and Affected Products (C/AP) list is in progress.

Proposed SGE's:

Antonio Fojo

Michael Menefee

Proposed Patient Representative:

Mr. Gavin

Discussion: Clearance is still pending. The team is targeting a mid-January consult.

8. **Additional Items or Issues:** None.

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/s/

DEANNE R VARNEY
12/17/2014

Varney, Deanne

From: Varney, Deanne
Sent: Monday, December 15, 2014 2:50 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 / Clinical Information Request

Hi Susan,

Please see the below clinical information request. Please confirm receipt and provide a response as soon as possible.

Please submit an analysis and a listing(by USUBJID) of patients who had decreased ejection fraction (as analyzed by echocardiographic measurement) of CTCAE Grade 3 and above in Study 303 and summarize it by the following:

- Description of the event if available (study day that it occurred, other concomitant AE's)
- Dose at which event occurred?
- Whether evidence exists that the event was reversible or not....if so with what intervention?
- Was lenvatinib dose reduced or discontinued?

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/15/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, December 09, 2014 12:28 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 - Clinical Pharmacology IR

Hello Susan,

The clinical pharmacology team has the below information requests. Please provide a response to me via email by COB on Monday, December 15, 2014, and follow with a formal submission to your NDA.

Reference is made to your Response to Clinical Information Request submitted on November, 17, 2014. Your submission included summary of findings included in Module 1.11.3 and datasets/codes included in Module 5.3.3.5. Additionally we request you submit the following:

1. Parameter Estimates from the models for ER analysis for AEs
2. Diagnostic plots / any other methodology used for model validation
3. A brief description of the methodology for ER analysis.

If you have submitted any of the above, please direct us to the correct Module for the submission.

Please confirm receipt and let me know should you have any questions.

Thank you!
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/09/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, December 09, 2014 10:59 AM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 / Clinical Information Request

Hi Susan,

Please see the below requests for information from the clinical team regarding lenvatinib NDA 206947. Please provide a response to me via email ASAP, and follow with a formal amendment to your NDA.

1. Please submit an analysis of the per-patient incidence of Grade 2 adverse events reported in the randomized portion of Study 303 (with data cut off of Mar 15,2014) by MedDRA preferred term that led to:
 - i. Lenvatinib discontinuations
 - ii. Lenvatinib dose reductions
 - iii. Lenvatinib dose interruptions
2. Please submit an analysis of the distribution (including number and percentage on each arm) of the 3 RAI refractory criteria that qualified patients as being RAI refractory in study 303.
3. Please submit an analysis (number and percent) of the baseline demographics of all the 1108 patients in the safety database with regard to tumor type (thyroid and other), median age, range of doses studied, duration of exposure etc.
4. Please provide a narrative, if available, for patient SUBJID 20610261008 (liver failure).

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/09/2014



NDA 206947

**METHODS VALIDATION
MATERIALS RECEIVED**

Eisai, Inc.
Attention: Susan Mayer, Director Global Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Susan Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lenvatinib capsules and to our November 3, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 3, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/03/2014

Varney, Deanne

From: Varney, Deanne
Sent: Monday, December 01, 2014 3:15 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 - Clinical Pharmacology Information Request

Hello Susan,

We have the following clinical pharmacology information request for NDA 206947. Please provide a response by 9 AM EST Monday, December 8, 2014.

Regarding your PBPK report, provide the model files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files, .cmp, .lbr, and .wks). These files should be executable by the FDA reviewers using Simcyp. Simulation outputs should be submitted as MS Excel files.

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/01/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, November 25, 2014 10:28 AM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 / Amendment to Due Date for Clinical Pharmacology Data Requested During MidCycle Communication

Hello Susan,

As agreed subsequent to the November 19, 2014, midcycle communication teleconference for lenvatinib, the requested data regarding sampling times, dosing times, and duration of treatment with pH elevating agents relative to dosing with lenvatinib will be submitted to NDA 206947 by December 1, 2014, rather than November 26, 2014, as previously agreed under Item 2b in the midcycle communication minutes.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
11/25/2014



NDA 206947

MID-CYCLE COMMUNICATION

Eisai, Inc.
Attention: Susan Mayer
Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lenvatinib.

We also refer to the teleconference between representatives of your firm and the FDA on November 19, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: November 19, 2014

Application Number: NDA 206947
Product Name: Lenvatinib
Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Applicant Name: Eisai, Inc.

Meeting Chair: Steven Lemery
Meeting Recorder: Deanne Varney

FDA ATTENDEES

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Monica Hughes, CPMS
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Stephanie Aungst, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Liang Zhou, CMC Team Leader
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader
Robert Schuck, Clinical Pharmacology/Genomics Reviewer
Okpo Eradiri, Biopharmaceutics Reviewer
Miriam Dinatale, Pediatric and Maternal Health Reviewer
Tracy Salaam, Pharmacovigilance Team Leader
Naomi Redd, Risk Management Acting Team Leader
Patrick Zhou, Eastern Research Group
Virginia Behr, CDER Ombudsman

APPLICANT ATTENDEES

Nancy Bower, Senior Director, Global Regulatory Affairs - Nonclinical
Corina Dutcus, Executive Director, Clinical Research, Oncology

James Ferry, Vice President & Head Clinical Pharmacology, TM and Modeling
Matthew Guo, Executive Director, Biostatistics, Oncology
Anubha Gupta, Associate Director, Clinical Pharmacology
Kenichi Nomoto, President Oncology
Alton Kremer, Deputy President, Oncology
Monica Lee, Director, Global Regulatory Affairs - CMC
Simon Lin, Director, Statistical Programming - Oncology
Susan Mayer, Director, Global Regulatory Affairs - Oncology
Carrie Mazzrillo, Global Regulatory Affairs - Submissions Manager
Martina Struck, President, Global Regulatory Affairs
Dimitris Voliotis, VP Clinical Research, Oncology
Sang Wong, Vice President, Global Regulatory Affairs - Oncology
Junming Zhu, Director Biostatistics, Oncology
Rolf Linke, MD, CMO SFJ Pharmaceuticals, Inc.

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical:

- a. The main clinical issue is determining whether a lower dose of lenvatinib might confer a favorable risk/benefit profile with less toxicity.

Discussion: FDA noted that a lower starting dose of lenvatinib will not be requested in product labeling. This issue identified by the Agency will be addressed via the proposed post-marketing study that will be discussed during the upcoming Type C meeting under IND 113656.

Clinical Pharmacology:

- b. Concomitant pH elevating agents appear to have a marked effect on the systemic exposure of lenvatinib.

Discussion: FDA noted that

(b) (4)

FDA noted that

Eisai attempted to address this via population pharmacokinetics (PK); however, FDA does not think this is sufficient. FDA requested that Eisai conduct a dedicated study to evaluate this effect.

Subsequently, Eisai stated that over 200 study subjects have received proton pump inhibitors (PPI's), H2 blockers, or antacids, and there is reliable data to make a decision whether the (b) (4) translates to an exposure effect in patients taking pH elevating agents. Eisai requested additional clarification for why the available data is not adequate.

FDA acknowledged the available data, and requested that Eisai provide all additional data regarding sampling times, dosing times and duration of treatment with the pH elevating agents relative to dosing with lenvatinib.

Eisai confirmed that they will provide the requested data; however, they are not sure the dosing times were recorded. Eisai will provide a response by November 26, 2014.

FDA requested clarification on the data collected regarding administration of concomitant medication. Eisai noted that different information was collected in different studies. Eisai will provide all information available on a study-by-study basis.

Statistics:

- c. Overall survival (OS) analysis using rank-preserving structural failure time (RPSFT).

Discussion: Eisai originally proposed to consider the OS analysis using the RPSFT model as the primary analysis in the SAP although the RPSFT model was not stated in the protocol. FDA considers the OS analysis using a stratified log-rank test as the primary analysis for regulatory purposes after reviewing the application. Since Eisai provided the overall survival results based on a stratified log-rank test in the proposed label, FDA no longer considers this an issue.

CMC:

- d. Request for clarification regarding whether the capsules administered to patients in the 303 study are the same as the capsules to be marketed under the NDA.

Discussion: Eisai confirmed that the formulations are identical.

Additional Issues Discussed:

- e. FDA noted that there is potential concern regarding the proposed proprietary name of Lenvima in regards to look-alike issues with another drug. Eisai should review other possible proprietary names to prepare for the possibility that the final decision (due November 26, 2014) determines that the proposed name is unacceptable.

3.0 INFORMATION REQUESTS

FDA inquired into the status of the CMC information request sent on November 14, 2014. Eisai stated that they are on target to provide a response by the requested date of November 26, 2014.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

FDA noted that risk issues will be communicated via the product labeling.

5.0 ADVISORY COMMITTEE MEETING

FDA noted that as previously discussed, this application will not be presented to the Oncology Drugs Advisory Committee (ODAC).

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

FDA informed Eisai that proposed labeling will be sent by January 16, 2015, and that the late cycle meeting is scheduled as a face-to-face meeting on February 4, 2015.

7.0 MISCELLANEOUS/WRAP-UP

- a. FDA noted that the randomized component of the expanded access study has caused some barriers in study initiation (as noted by Eisai during the Application Orientation Meeting), and inquired if the study could potentially be revised to be a one-arm study using 24 mg. Eisai stated that five sites have been initiated and have started enrolling subjects, and an additional site will be initiated by the end of 2014. Therefore, Eisai would prefer not to revise the study at this time, because this could further delay enrollment into the expanded access study. FDA agreed with this determination.
- b. FDA noted that there is some interest in discussing lenvatinib at a future pediatric sub-committee of ODAC. Eisai expressed their understanding of this and welcomed the opportunity for such a discussion.
- c. FDA noted that there is the possibility of an early action by one or maybe two months. Eisai noted that they would be ready for product launch in the event that

an earlier action is taken, with the possible exception of a change in the proprietary name. FDA stated that if the name is ultimately identified as unacceptable, Eisai should request a teleconference with the Division of Medication Error Prevention and Analysis (DMEPA) to discuss any questions and any new proposed names.

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/s/

DEANNE R VARNEY
11/25/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206947

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Esai, Inc.
155 Tice Boulevard
Woodcliff Lake, NJ 07677

ATTENTION: Susan Mayer
Director, Global Regulatory Affairs

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) dated August 14, 2014, received August 14, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lenvatinib Capsules, 4 mg and 10 mg.

We also refer to your August 28, 2014, correspondence, received August 28, 2014, requesting review of your proposed proprietary name, Lenvima.

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

Lenvima is orthographically similar to the currently marketed product, Levemir (Insulin detemir). With respect to the orthographic similarity of the names, both names are seven characters in length, begin with the similar letter strings, “Le” vs. “Le” and the infixes for the name pair are similar, “vim” vs. “vem”. Furthermore, FDA’s Phonetic and Orthographic Computer Analysis (POCA) calculates a combined score of 62% for Lenvima and Levemir, which further suggests that the names have look-alike similarity. Additionally, during the current evaluation of the proposed name, one participant in the inpatient written portion of the FDA Prescription Simulation study misinterpreted the name Lenvima as “Levemir,” a drug currently marketed for the treatment of diabetes mellitus. The sample below was used as part of the Prescription Simulation study where Lenvima was misinterpreted as “Levemir.”

Lenvima 14mg PO QD

Given this finding, we carefully analyzed the product characteristics to determine whether or not the name similarity would be likely to lead to errors in the usual practice setting. Although Lenvima will be available in multiple strengths, both Lenvima and Levemir share the same frequency of administration (once daily) and have usual doses

with numeric similarities. Lenvima is dosed as 24 mg, 20 mg, 14 mg, or 10 mg. Levemir dosing is based on patient requirements and doses of 24 units, 20 units, 14 units, or 10 units are conceivable doses that are used in the maintenance of glycemic control in diabetes mellitus.

We note that Lenvima is a capsule administered orally and Levemir is solution administered as an injection. Although the products have different routes of administration (oral vs. subcutaneous injection) and dosage forms, the single route of administration and the dosage form could be omitted from a written prescription. We also acknowledge that the units of measure are different for these products (units vs. mg), however post-marketing surveillance of other drug products supports this conclusion. Specifically, we have reviewed reports of errors involving confusion between similarly named drug products, even when dosage form, route of administration and units of measure differs.^{1,2,3}

We acknowledge that this determination differs from our previous evaluation and conclusion communicated in the letter dated July 9, 2013. We have reached a different determination with respect to the safety of your proposed name primarily because of the new safety information identified in the FDA Prescription Simulation Study. In our previous evaluation of Lenvima, we identified Levemir as having some similarity to Lenvima but we concluded at the time that orthographic and strength differences in the names would distinguish these names in written communications. At the time of our previous analysis, we had conducted simulation studies and there were no misinterpretations of Lenvima as Levemir in those simulation studies.

Several reasons could explain why our previous name simulation studies did not produce a misinterpretation of Lenvima as “Levemir”. The simulation studies were performed using different handwriting and voice samples of the proposed name and the current simulation study was conducted using a new group of FDA participants. Both or either of these changes could contribute to differences in the results of the simulation studies.

Additionally, name simulation studies are not designed to detect errors with statistical significance since such studies would call for a large sample size. Thus, a negative finding (i.e. no name confusion) from a simulation study using a small sample size does not provide assurances that errors are unlikely to occur. However, FDA believes our simulation studies have good predictive value when an error does occur because the likelihood of observing an error in a small study is low, and therefore an occurrence

¹ Institute for Safe Medication Practices. Safety briefs: Advair-Advicor mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2003; 2(8): 1-2.

² Institute for Safe Medication Practices. Safety briefs: Include purpose on Rx. ISMP Med Saf Alert Acute Care. 2011;16(17):1-2.

³ Institute for Safe Medication Practices. Errors and near misses prompt warning to practitioners and a call to rename CELEBREX. ISMP Med Saf Alert Acute Care. 1999;4(7):1.

within this study is likely to predict errors that will occur between Lenvima and Levemir in actual use. Thus, this new information represents a safety concern that prompted us to reverse the conclusion previously reached on the acceptability of the name, Lenvima.

Collectively, our analysis of the name similarity, post-marketing experience with other reported errors, and the prescription simulation study misinterpretation lead us to conclude that the name Lenvima is vulnerable to confusion with Levemir and would result in harmful errors. Thus, we find your name unacceptable.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you require additional information on developing proprietary names for drugs, we recommend that you review the draft Guidance for Industry, *Best Practices in Developing Proprietary Names for Drugs*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Deanne Varney, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
11/20/2014

TEAM MEETING MINUTES

November 19, 2014

New NDA 206947
Lenvatinib
Eisai

Submission Date: August 14, 2014
Received Date: August 14, 2014
PDUFA Date: April 14, 2015

Proposed Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Core Review Team:

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Stephanie Aungst, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Gaetan Ladouceur, CMC
Amit Mitra, CMC
Liang Zhou, CMC Team Leader
Ali Al Hakim, CMC (Branch Chief)
Teicher Agosto, CMC (ONDQA RPM)
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader
Robert Schuck, Clinical Pharmacology/Genomics Reviewer
Rosane Charlab Orbach, Clinical Pharmacology/Genomics Team Leader
Okpo Eradiri, Biopharmaceutics Reviewer
Angelica Dorantes, Biopharmaceutics Team Leader
Jessica Cole, Quality Microbiology Reviewer

Consults:

Nick Senior, OPDP / Jessica Cleck Dereneck, OPDP TL
Nathan Caulk, PLT / Barbara Fuller, PLT TL
Afrouz Nayernama, DPV / Tracy Salaam, DPV TL
Carolyn Yancey, DRISK / Naomi Redd, DRISK Acting TL
Otto Townsend, DMEPA / Alice Tu, DMEPA TL
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL
Lauren Iacono-Connors, OSI / Janice Pohlman, OSI TL
Miriam Dinatale, PMHS / Jeanine Best, TL / Alyson Karesh, Acting TL / Vicki Moyer, P

AGENDA ITEMS:

1. Review Status:

- Priority Review (PDUFA V --- 8 month review)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of lenvatinib has been conducted under INDs (b) (4) and 113656

2. Reminder of Milestone Dates for 8-Month Priority Review Clock:

Milestone	8 month review
Acknowledgment Letter	August 28, 2014 <i>Issued August 28, 2014</i>
Filing Issues Identified Letter	October 13, 2014 <i>Issued October 10, 2014</i>
Mid-Cycle Meeting	Month 3 – November 12, 2014 <i>Scheduled November 4, 2014</i>
Mid-Cycle Communication	Month 3.5 – November 27, 2014 <i>Scheduled November 19, 2014</i>
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 – January 16, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Month 5.25 - January 23, 2015
Late Cycle Meeting Target Date	Month 6 if no AC – February 12, 2015 <i>Scheduled February 4, 2015</i>
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 – January 14, 2015 Month 5.1 – January 17, 2015 Month 7 – March 19, 2015 1.5 weeks pre-action – April 3, 2015 April 14, 2015
Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action – March 10, 2015 <i>Scheduled February 25, 2015</i>
Compile and circulate Action Letter and Action Package	3 weeks pre-action – March 24, 2015
FINAL Action Letter Due	April 14, 2015

NOTE: The team will target an early action date of late February or early March. The CDTL, division director, and office director reviews will need to be completed prior to the goal dates noted in the table above.

Discussion:

- CDTL will target a review due date of January 30, 2015.
- Division Director will target a review due date of February 13, 2015.
- The wrap-up meeting will be moved up to late January or very early February.

3. **Reminder regarding midcycle communication teleconference:** The purpose of this call will be to update Eisai on:

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for late-cycle meeting
- Updates regarding plans for the AC meeting
- Other projected milestone dates for the remainder of the review cycle

Discussion: We will inform Eisai that we might target an earlier action by one or possibly two months, and inquire if that would pose any product launch issues.

4. **Review Issues:**

- Clinical:** No new issues.
- Statistics:** After review of the label it appears that Eisai used the log-rank test results, not RPSFT, so this is no longer an issue that requires discussion during the midcycle communication.
- Clinical Pharmacology:** No new issues.
- Pharmacometrics:** The exposure-response curves do show trends that a lower dose might be less toxic.
- Genomics:** No new issues.
- Nonclinical:** No new issues.
- CMC:** CMC sent an information request on November 14, 2014, and the response is pending (due November 26, 2014).
- Biopharmaceutics:** No updates at this time.
- Microbiology:** Review is complete with no outstanding issues.
- Regulatory:** No issues.

5. **Inspections:**

a. **Clinical Site Inspections:**

Planned inspections:	Scheduled dates for inspection	Status	Preliminary Outcome	Site Number
CRO: (b) (4)	October 9 th -16 th , 2014	Completed	NAI. No major issues.	N/A
Dr. Shah (Ohio)	October 6-17, 2014	Completed	VAI. No major issues.	1018
Dr. Francoise Bonichon (Bordeaus France)	December 1-5, 2014	Scheduled		1401
Dr. Christelle Fouchardiere (Lyon France)	November 17-21, 2014	Scheduled		1402
Dr. Hiroto Ishiki (Chiba Japan)	December 1-5 2014	Scheduled		1201
Dr. Eun Lee (S. Korea)	December 8-12, 2014	Scheduled		3001

Discussion: All inspections are on schedule and there are no updates at this time.

b. **Manufacturing Site Inspections:**

Establishment Name	EER Creation Date	Country Code	Responsibilities	Profile Code	PAI Status	Anticipated Inspection Dates	Compliance Status
(b) (4)	09.22/2014	USA	Packaging	CHG	Acceptable-Based on Profile	N/A	AC
PATHEION INC. TORONTO REGION OPERATIONS	09.22/2014	CAN	Drug Product Manufacturing and Testing	CHG	Pending	January 2015	PN
EISAI COMPANY, LTD.	09.22/2014	JPN	Drug Substance Manufacturing and Testing	(b) (4)	Pending	November 2014	PN
EISAI INC	09.22/2014	USA	Drug Product Testing	CTL	Pending	Under evaluation by District	PN

PATHEON INC.- BURLINGTON CENTURY OPERATIONS	09.22/2014	CAN	Drug Product Testing	CTL	Pending	January 2015	PN
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Discussion: OMPQ does not intend to inspect the Patheon-Burlington facility, and will make an acceptable decision based on profile. ONDQA will follow-up with OMPQ regarding the final decision of whether or not the site will be inspected.

6. **Upcoming Meetings:**

- **Mid-Cycle Communication Sponsor Tcon:** November 19, 2014
- **Labeling Meetings:**
 - a. December 1, 2014: Clinical and Statistics - Sections 1, 14
 - b. December 2, 2014: Clin Pharm and Clinical – Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3
 - c. December 8, 2014: Clinical, CMC, DMEPA – Sections 3, 11, 16
 - d. December 10, 2014: Clinical – Sections 4, 5, 6, 17
 - e. December 11, 2014: Clinical, Nonclinical, Maternal Health – Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13
 - f. January 12, 2015: If needed
- **Monthly Team Meetings:**
 - a. October 23, 2014
 - b. November 19, 2014
 - c. December 17, 2014
 - d. January 21, 2015
 - e. February 16, 2015
 - f. March 19, 2015
 - g. April 6, 2015
- **Late Cycle Meeting:** February 4, 2015
- **Wrap- Up Meeting:** February 25, 2015.

Discussion: The wrap-up meeting will be moved up to late January or early February.

7. **ODAC: Not Required**

8. **SGE's:** The proposed SGE's and patient representative listed below have agreed to participate. The Competing and Affected Products (C/AP) list is in progress.

Proposed SGE's:
Antonio Fojo
Michael Menefee

Proposed Patient Representative:

(b) (6)

Discussion: A mid-January consult will be targeted.

8. **Additional Items or Issues:** None to discuss.

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/s/

DEANNE R VARNEY
11/19/2014



NDA 206947

INFORMATION REQUEST

Eisai Inc.
Attention: Susan Mayer
Director, Global Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lenvatinib capsules.

We are reviewing the Quality section of your submission and have the following information requests. We request a prompt written response by November 26, 2014, in order to continue our evaluation of your NDA.

Drug Product

1. Discuss if lot-to-lot variability [REDACTED] (b) (4) would have an adverse impact on product quality. If there is an adverse impact, describe your control strategy.
2. Provide a risk assessment to assure that the [REDACTED] (b) (4) [REDACTED] in the drug product throughout the life cycle of the product.
3. As a control strategy, adopt a limit test for level [REDACTED] (b) (4) in the drug product and include it in the drug product specification. Submit the analytical method and its validation.
4. Provide the results from the [REDACTED] (b) (4) studies as a part of the analytical method development.
5. Provide the specifications for the [REDACTED] (b) (4) lidding foil. Adopt a seal integrity test for the blister package. Also, establish an acceptance criterion for [REDACTED] (b) (4) Provide the

physical-chemical test data and assure its compliance with physicochemical tests, USP <661>.

6. Provide the CFR citation for food contact of the [REDACTED] (b) (4), its description including the chemical composition and specification.

Labeling

1. Revise the “Description” section of the PI with dissociation constant and partition coefficient information; otherwise, justify.
2. Revise the inactive ingredient list of the SPL as follows: 1) include hydroxypropyl cellulose, talc, and hypromellose, 2) replace “hydroxypropyl cellulose (type H)” with “[REDACTED] (b) (4) [REDACTED]”.

If you have any questions, call Teicher Agosto, Regulatory Project Manager, at (240) 402-3777.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim, PhD
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Ali H. Al-
Hakim -S
Digitally signed by Ali H. Al-
Hakim -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300
093815, cn=Ali H. Al- Hakim -S
Date: 2014.11.14 13:28:33 -05'00'

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, November 05, 2014 12:12 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 Statistical IR

Hello Susan,

We have the following statistical information request related to your new NDA 206947. Please provide a response to me via email by **COB on Wednesday, Monday, November 17, 2014**, and follow with a formal submission to your IND.

1. When using the rank preserving structural failure time (RPSFT) model (Robin and Tsiatis, 1991) in your OS analysis, verification of some assumptions is usually needed. However, we have not found any analysis of verifying the assumptions in the submission. Please provide the information, if available.
2. Please explain why an un-stratified log-rank test is used to calculate p-value instead of a stratified log-rank test in Step 4 of Specs and Algorithm Implementation of RPSFT method in APPENDICES from Reviewersguide.pdf.

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
11/05/2014



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

Memorandum

Date: November 4, 2014
From: Deanne Varney, DOP2/OHOP/CDER
Subject: Midcycle Meeting Minutes: Lenvatinib NDA 206947

NME Application: NDA 206947

Product: lenvatinib

Received Date: August 14, 2014

PDUFA Date: April 14, 2015

Sponsor: Eisai, Inc.

Proposed Indication: Radioiodine-refractory differentiated thyroid cancer

This midcycle meeting for NDA 206947 was a face-to-face internal FDA meeting.

Attendees included: Richard Pazdur, Patricia Keegan, Steven Lemery, Abhilasha Nair, Janet Jiang, Kun He, Jun Yang, Hong Zhao, Anshu Marathe, Liang Zhao, Emily Fox, Stephanie Aungst, Whitney Helms, Amit Mitra, Liang Zhou, Okpo Eradiri, Robert Schuck, Rosane Orbach Charlab, Robert Wittorf, Jeff Summers, Nicholas Senior, Monica Hughes, Ingrid Fan, Jennie Chang, Leigh Marcus, Hui-Lee Wong, Miriam Dinatale, Nathan Caulk, Naomi Redd,

Discussion Items:

Slides were presented by (in order):

- RPM Regulatory
- Clinical and Statistical, Efficacy & Safety
- Clinical Pharmacology
- Non-Clinical
- CMC and Biopharmaceutics

Benefit-Risk Overview (summarized from Clinical):

- PFS of 18.3 months vs. 3.6 months; ORR of 64%; OS analysis shows trend favoring lenvatinib
- The 24 mg dose might not maximize the risk-benefit ratio, as there were significant dose reductions and dose interruptions at the 24 mg dose. A potential PMR will be to determine if a lower dose has similar efficacy with improved safety.

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/s/

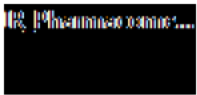
DEANNE R VARNEY
11/04/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, November 04, 2014 2:49 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 - Clinical Pharmacology IR

Hello Susan,

The clinical pharmacology team as the attached information request. Please provide a response by COB on Friday, November 14th.



Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

Your submission dated, August 14th 2014, to NDA 206947, is currently under the review.

Reference is made to your Population Analysis Report (CPMS-E7080-007R-v1) titled "*Population Pharmacokinetic Analysis of Lenvatinib (Pooled Data) and Pharmacokinetic/Pharmacodynamic Analyses of Lenvatinib Efficacy, Biomarker (Study E7080-G000-303) and Safety (Studies E7080-G000-201, E7080-G000-303, E7080-J081-208) in Subjects with Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancer*". We have following information request. Please submit the responses by November 14, 2014. Datasets, NONMEM control streams, and scripts used to generate analyses and plots should be provided for the analyses requested. Data files should be submitted as SAS transport files (eg, Data1.xpt) and other files be submitted as ASCII text files (eg, myfile_ctl.txt, myfile_out.txt). You can schedule a teleconference with the Pharmacometrics review team if you have clarifying questions regarding the information request.

1. Based on your population PK model, provide boxplots for steady state AUC and Cmin for 24 mg QD, 20 mg QD and 14 mg QD dose levels. Summarize 5th, 25th, 50th, 75th and 95th percentiles of AUC and Cmin in a table.
2. Exposure-response (ER) analyses for adverse events (AEs).
 - a. Generate summary tables using your NONMEM datasets for proportion of patients experiencing any grade or different grades of AEs in the placebo and treatment arms. Compare proportions of patients experiencing any or different grade AEs as derived from NONMEM datasets to results derived from relevant clinical study reports (for example-Table 32 and 33 of CSR of study 303). Provide your justification on any discrepancies.
 - b. Figure 8-49 of your report shows the percentage of Grade 3 hypertension events vary between 10-20% across the 4 quartiles. This is also reflected in plots 8-50 and 8-51. Our understanding is that the percentage/probability represents the ratio of number of observations of Grade 3 hypertension events to the total number of all grade hypertension events. If this is the case, the analysis will not correctly reflect the percentage of patients who experienced Grade 3 hypertension events. Based on the clinical study report (CSR) of studies 303, 201 and 208, the Grade 3 hypertension were 42.5%, 10.3% and 54.5% respectively, which is higher than your current analysis. We recommend that you conduct ER analysis for hypertension and proteinuria in terms of proportion of patients with AEs as reported in the study reports. In addition, conduct exposure-response (ER) analysis for diarrhea, nausea and vomiting.
 - c. Your current analysis included data from the placebo arm. It appears from figures 8-50, 8-51 and 8-53 that the ER relationship is driven primarily by the placebo data. Please conduct ER analysis using data from the treatment arm only.

- d. In addition to the exposure metrics that you have selected, conduct ER analysis for hypertension, proteinuria, diarrhea, nausea and vomiting using AUC based on 1) starting dose and 2) AUC based on dose intensity where dose intensity is calculated as total dose up to the time of the adverse event divided by time. Summarize the observed AEs as well as distributions of demographics/covariates by exposure quartiles. Please also provide information on proportion of patients with dose interruption or dose reduction in each quartile.

The goal of the additional analysis is to predict the proportion of patients with AEs (any grade/grade 3 or higher) at exposures that are likely to be achieved at 24 mg QD, 20 mg QD and 14 mg QD.

3. ER analyses for PFS

- a. Generate Kaplan-Meier curves for PFS stratified by the final dose level after dose reduction. If differences are observed between the three dose levels (24 mg QD, 20 mg QD and 14 mg QD), conduct Cox regression analysis adjusting for confounding factors to ascertain if the dose is a predictor for efficacy.
- b. Generate Kaplan-Meier curves for PFS stratified by time to first dose reduction. If differences are observed, conduct Cox regression analysis adjusting for confounding factors to ascertain if time to first dose reduction is a predictor for efficacy.

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/s/

DEANNE R VARNEY
11/04/2014



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

Memorandum

Date: November 4, 2014
From: Deanne Varney, RPM, DOP2/OHOP/CDER/FDA
Subject: NDA 206947

TELECONFERENCE

Sponsor Attendees:

Monica Lee, Director Global Regulatory Affairs, CMC
Susan Mayer, Regulatory Core Function Unit
Hope Tuck, Principal Manager, External Manufacturing Quality Operations (EMQO)

FDA Attendees:

Deanne Varney
Patricia Keegan
Robert Wittorf
Amit Mitra
Steven Lemery
Abhilasha Nair

Objectives:

Request clarification from Eisai on the drug product (DP) manufacturing, testing and packaging sites outlined in NDA 206947.

Discussion:

FDA requested clarification on the facilities that will be manufacturing, testing and packaging the drug product. Eisai confirmed that Module 3.1 of the NDA is correct as submitted. Drug product is manufactured at the Toronto Patheon site for the bulk capsules. Chemical and Microbiological release testing is performed at Patheon (Burlington Region Operations), Patheon (Toronto Region Operations). Eisai at Research Triangle Park (RTP) will be performing chemical and microbiological testing for both release and stability testing. [REDACTED] ^{(b) (4)} is the contract blister pack manufacturer. FDA requested clarification regarding which Patheon site is performing which roles. Eisai confirmed that manufacturing occurs at the Toronto Patheon site, and that testing has been done at the Burlington site for process validation batches; however, the Burlington site will potentially be closed by end of December 2014, with all methods being transferred to the Toronto site. Eisai did mention that the timing of closing the Burlington site has been delayed a few times and another batch of lenvatinib could have the option of being tested at the Burlington or Toronto facility. Eisai confirmed that the same analysts and same equipment will be used at the Toronto site as has been used at the Burlington site. Eisai also

confirmed that all validation documentation and data from Burlington will be available at Toronto site upon the Burlington site closing.

FDA requested clarification on where the initial development of analytical methods occurred. Eisai stated that the development group in Japan performed the analytical development and it was then transferred to both Patheon facilities and to Eisai, RTP. Eisai stated that there is no difference in testing methods between either Patheon facility or the Eisai RTP site.

FDA requested Eisai submit an amendment to NDA 206947 which reflects what drug product sites are being used in commercial manufacturing. The amendment should also clarify that the Burlington site has closed and responsibilities have been transferred to Toronto. Eisai asked if they can close the Burlington site post-approval. FDA stated that the 356h should list all facilities involved in the commercial manufacturing process of the drug product, including testing facilities in order to assist us in the reviewing the application. Eisai asserted that the Burlington site should remain on the 356h because the site is performing drug product testing for NDA 206947. FDA agreed that no amendment is required if the facilities listed in the current 356h form and module 3.1 adequately list all facilities involved in commercial manufacturing, testing and packaging of the drug product. Eisai confirmed the correctness of the 356h form pertaining to the list of drug product facilities and no amendment will be submitted to the FDA.

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/s/

DEANNE R VARNEY
11/04/2014



NDA 206947

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Eisai
Attention: Susan Mayer
Director Global Regulatory Affairs
155 Tice Boulevard
Woodcliff Lake, NJ 07677
FAX: (201) 673-4620

Dear Susan Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lenvatinib capsules 4 mg and 10 mg.

We will be performing methods validation studies on Lenvatinib capsules 4 mg and 10 mg, as described in NDA 206947.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Drug Substance
 Related substances
 Genotoxic impurities
Drug Product
 Related substances

Samples and Reference Standards

1 g lenvatinib mesilate drug substance
1 g lenvatinib mesilate reference standard
50 Lenvatinib capsules 4 mg
50 Lenvatinib capsules 10 mg
20 mg of related substance (b) (4) if available
20 mg of related substance (b) (4) if available
500 mg of (b) (4)
250 mg of (b) (4)

Equipment

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
11/03/2014

TEAM MEETING MINUTES

October 23, 2014

New NDA 206947
Lenvatinib
Eisai

Submission Date: August 14, 2014
Received Date: August 14, 2014
PDUFA Date: April 14, 2015

Proposed Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Core Review Team:

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Stephanie Aungst, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Gaetan Ladouceur, CMC
Amit Mitra, CMC
Liang Zhou, CMC Team Leader
Ali Al Hakim, CMC (Branch Chief)
Teicher Agosto, CMC (ONDQA RPM)
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader
Robert Schuck, Clinical Pharmacology/Genomics Reviewer
Rosane Charlab Orbach, Clinical Pharmacology/Genomics Team Leader
Okpo Eradiri, Biopharmaceutics Reviewer
Angelica Dorantes, Biopharmaceutics Team Leader
Jessica Cole, Quality Microbiology Reviewer

Consults:

Nick Senior, OPDP / Jessica Cleck Dereneck, OPDP TL
Nathan Caulk, PLT / Barbara Fuller, PLT TL
Afrouz Nayernama, DPV / Tracy Salaam, DPV TL
Carolyn Yancey, DRISK / Naomi Redd, DRISK Acting TL
Otto Townsend, DMEPA / Alice Tu, DMEPA TL
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL
Lauren Iacono-Connors, OSI / Janice Pohlman, OSI TL
Miriam Dinatale, PMHS / Jeanine Best, TL / Alyson Karesh, Acting TL / Vicki Moyer, PM

AGENDA ITEMS:

1. Review Status:

- Priority Review (PDUFA V --- 8 month review)
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of lenvatinib has been conducted under INDs (b)(4) and 113656

2. Reminder of Milestone Dates for 8-Month Priority Review Clock:

Milestone	8 month review
Acknowledgment Letter	August 28, 2014 <i>Issued August 28, 2014</i>
Filing Issues Identified Letter	October 13, 2014 <i>Issued October 10, 2014</i>
Mid-Cycle Meeting	Month 3 – November 12, 2014 <i>Scheduled November 4, 2014</i>
Mid-Cycle Communication	Month 3.5 – November 27, 2014 <i>Scheduled November 19, 2014</i>
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 – January 16, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Month 5.25 - January 23, 2015
Late Cycle Meeting Target Date	Month 6 if no AC – February 12, 2015
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 – January 14, 2015 Month 5.1 – January 17, 2015 Month 7 – March 19, 2015 1.5 weeks pre-action – April 3, 2015 April 14, 2015
Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action – March 10, 2015
Compile and circulate Action Letter and Action Package	3 weeks pre-action – March 24, 2015
FINAL Action Letter Due	April 14, 2015

3. Midcycle Preparation: Any questions regarding planned presentations?

Discussion: The team was reminded to provide draft slides to the RPM by October 29, 2014, and to keep presentations to no more than 10 slides per discipline.

4. **Reminder regarding midcycle communication teleconference:** Each discipline should send the RPM a list of the issues that require discussion in advance of the meeting (by November 12th). The purpose of this call will be to update Eisai on:

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for late-cycle meeting
- Updates regarding plans for the AC meeting
- Other projected milestone dates for the remainder of the review cycle

Discussion: No additional discussion occurred during the meeting.

5. **Review Issues:**

- a. **Clinical:** None to discuss.
- b. **Statistics:** None to discuss.
- c. **Clinical Pharmacology:** None to discuss.
- d. **Pharmacometrics:** None to discuss.
- e. **Genomics:** None to discuss.
- f. **Nonclinical:** None to discuss.
- g. **CMC:** None to discuss.
- h. **Biopharmaceutics:** None to discuss.
- i. **Microbiology:** None to discuss.
- j. **Regulatory:** None to discuss.

6. **Inspections:**

- a. **Clinical Site Inspections:** Tentative clinical site inspections schedule?

Discussion: Two sites inspections have been completed with no issues found. International site inspections are scheduled for November and early December.

b. **Manufacturing Site Inspections:** Most recent compliance status?

Discussion: No updates were available at the meeting.

7. **Upcoming Meetings:**

- **Mid-Cycle Meeting:** November 4, 2014.
- **Mid-Cycle Communication Sponsor Tcon:** November 19, 2014
- **Labeling Meetings:**
 - a. December 1, 2014: Clinical and Statistics - Sections 1, 14
 - b. December 2, 2014: Clin Pharm and Clinical – Sections 2, 7, 8.5, 8.6, 8.7, 12.2, 12.3
 - c. December 8, 2014: Clinical, CMC, DMEPA – Sections 3, 11, 16
 - d. December 10, 2014: Clinical – Sections 4, 5, 6, 17
 - e. December 17, 2014: Clinical, Nonclinical, Maternal Health – Sections 5.1, 8.1, 8.3, 8.4, 12.1, 13
 - f. January 12, 2015: If needed
- **Monthly Team Meetings:**
 - a. October 23, 2014
 - b. November 19, 2014
 - c. December 17, 2014
 - d. January 21, 2015
 - e. February 16, 2015
 - f. March 19, 2015
 - g. April 6, 2015
- **Late Cycle Meeting:** TBD, By February 12, 2015
- **Wrap- Up Meeting:** TBD, By March 10, 2015.

Discussion: The team discussed the possibility of scheduling the late cycle and wrap-up meetings a couple of weeks before the target dates. The RPM will follow-up on this and schedule accordingly.

8. **ODAC: Not Required**

9. **SGE's:** The proposed SGE's and patient representative listed below have agreed to participate. The Competing and Affected Products (C/AP) list is in progress.

Proposed SGE's:
Antonio Fojo
Michael Menefee

Proposed Patient Representative:

(b) (6)

Discussion: No additional discussion occurred regarding the SGE's.

8. **Additional Items or Issues:** None to discuss.

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/s/

DEANNE R VARNEY
10/23/2014

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, October 23, 2014 1:51 PM
To: 'Susan_Mayer@Eisai.com'
Subject: RE: Lenvatinib NDA 206947 - Clinical Information Request

Hi Susan,

The clinical team has noted that the reviewer's guide is helpful, but that Eisai should still submit a document similar to the one submitted for the datasets ADAE ADSL ADEX and ADDS (response to question 6 part II) for the rest of the 303 ISS Analysis datasets (ADEXSL,ADCM etc.) as soon as possible. You can omit the variables already explained in the first 4 datasets for a faster response. Please also submit a document similar to this for the ISS Analysis datasets 5.3.5.3 (all studies combined) in 2-3 weeks .

Additionally please clarify the following in your response to Question 1 -Were the CTCAE grading used for **laboratory values** and **investigator reported terms** the same in Study 303?(i.e. both were coded to version 4.03?-please confirm). In the ISS reviewer's guide (page 6) it says that AE's were coded to version 4 and laboratory values to 4.03...is this statement an error?

Thank you for your responses and quick turnaround – much appreciated.

Regards,
Deanne

From: Susan_Mayer@Eisai.com [mailto:Susan_Mayer@Eisai.com]
Sent: Thursday, October 23, 2014 9:17 AM
To: Varney, Deanne
Subject: Fw: Lenvatinib NDA 206947 - Clinical Information Request

Hi Deanne,

Our dataset team has asked me to follow up regarding the last portion of the request in Question 6, " and follow up with the rest of the analysis datasets (in 2-3 weeks)" . Does the Reviewer's Guide provided yesterday suffice for the remaining datasets? If not, it will be very helpful if a list of dataset and the specific associated variables can be provided for us to clarify which datasets and associated variables need further clarification.

Thank you,
Susan

Susan Mayer
Regulatory Core Function Unit
Eisai Product Creation Systems
155 Tice Blvd.
Woodcliff Lake, NJ 07677
Tel: 201-949-4831
Fax: 201-746-3211

Email: susan_mayer@eisai.com

----- Forwarded by Susan Mayer/RIG/EisaiInc on 10/23/2014 09:07 AM -----

From: Susan Mayer/RIG/EisaiInc
To: Deanne.Varney@fda.hhs.gov
Date: 10/22/2014 05:21 PM
Subject: Fw: Lenvatinib NDA 206947 - Clinical Information Request

Hi Deanne,

Attached Please find our response to Question 6 (Part 1). Part 2 of Question 6 will be responded to shortly.

6. Although not discussed during our telephone conference, since the define file for Study 303 ISS analysis dataset with a cut off of March 2014 (Module 5.3.5.1) lacks clarity in defining most variables, please submit a reviewer's guide or separate document that explains what the terms/variables are in text and not in statistical computational terms. This would facilitate our expedited review of the application. Please submit this document for the datasets ADSL,ADAE,ADEX,ADDS first (as soon as possible) and follow up with the rest of the analysis datasets (in 2-3 weeks).

Attached please find a Reviewer's Guide and separate document which explains the terms/variables supporting the define file for Study 303 ISS analysis dataset (. ADSL,ADAE,ADEX,ADDS) as requested in Part 1 of this question.

Susan Mayer
Regulatory Core Function Unit
Eisai Product Creation Systems
155 Tice Blvd.
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----- Forwarded by Susan Mayer/RIG/EisaiInc on 10/22/2014 02:48 PM -----

From: Susan Mayer/RIG/EisaiInc
To: Deanne.Varney@fda.hhs.gov
Date: 10/20/2014 04:07 PM
Subject: Fw: URGENT REVIEW OF FDA RESPONSE - Due today by 3:00 PM

Hi Deanne,

Below, please find responses to questions 3 through 5. Please confirm receipt.

Best regards,
Susan

From: "Varney, Deanne" <Deanne.Varney@fda.hhs.gov>

To: "Susan_Mayer@eisai.com" <Susan_Mayer@eisai.com>
Date: 10/15/2014 02:29 PM
Subject: Lenvatinib NDA 206947 - Clinical Information Request

Hello Susan,

In follow-up to the teleconference this morning with the clinical team, please provide responses for the following issues discussed during the teleconference to me via email, and follow with a formal amendment to your NDA:

1. The MedDRA version that was used for AE coding for the different datasets and the CTCAE toxicity grading scale for adverse event and laboratory values grading.

All investigator terms were coded to MedDRA, version 16.1 in Module 2.7.4 (SCS) and the E7080-G000-303 Clinical Study Report .

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to assess the severity of TEAEs. For studies conducted earlier in development that used NCI CTCAE version 3.0, the data were recoded using version 4.03.

2. The contents of the Errata for the CSR for Study 303 and confirmation as to whether any of it changes the ultimate risk benefit profile (or information contained in product labeling) of lenvatinib for the proposed indication.

A summary of the errata reports appears below:

- Serum samples collected were tested for Thyroglobulin (Tg) concentrations using a commercially available ELISA (Enzyme Linked ImmunoSorbent Assay) kit. In the initial screen of the samples, tested without dilution, it was found that nearly one third had Tg concentrations beyond the highest point of the assay's dynamic range (300 ng/mL). Subsequent dilution and re-testing was required, and samples were re-tested. Results were updated and Appendix 16.2.14.2 was replaced.
-
- A total of 8 discrepancies were found after database lock (15 Nov 2013). The discrepancies were reviewed, and they were found not to impact the outcome of the analysis. It was determined that the database lock could be maintained and there was no immediate need for a database unlock. These discrepancies include typographical errors in dates (5 subjects), duplicate entries for batch numbers (1 subject), and prior VEGF therapy selected as "Yes" when it was actually "No" (2 subjects). This updated information is included in either the ISS dataset (15 Mar 2014) and/or the 120-Day Safety Update dataset (15 Jun 2014).
-
- When data from the 15-Mar-2014 cutoff date were compared to data from the 15-Nov-2013 CSR cutoff date, it was noted that changes were made by the site to the CSR data after the 15 Nov 2013 cutoff date. These are not data errors, just new information that the sites updated after the database was locked for the CSR. Examples include: minor changes in dates, uploading of lab data, changes in target/non-target lesion sizes, concomitant medications, and drug batch number discrepancies. This updated information (with the exception of efficacy and batch data) is included in either the ISS dataset (15 Mar 2014) and/or the 120-Day Safety Update dataset.

Based on this information, Eisai concludes that the data in these errata do not impact the safety outcome or change the risk/benefit assessment or information contained in the proposed product labeling.

Additionally, please provide a response to the following clinical requests and clarifications as soon as possible to me via email, and follow with a formal amendment to your NDA:

3. Please explain the following statement in page 11 of the Analysis Data Reviewers guide for Study 303 Mar 15,2014 cut off Module 5.3.5.1 : "For patients with Placebo in period 1 and Lenvatinib in Period 02 (Open Label), the data in period 02 are pooled in the analysis".

As per our agreement at the Pre-NDA Meeting on 25 March 2014, subjects who received lenvatinib in the OOL Phase (period 2) are pooled with the non randomized DTC subjects in the ISS. Period 1 includes placebo patients from the randomization phase, period 2 includes placebo subjects who received lenvatinib treatment in the OOL phase. Data from subjects in period 2 were pooled with data from subjects in the non randomized DTC population.

4. Are the datasets used for the safety progress report for Study 303 with a March 15,2014 cut-off the same as those that generated the summary of clinical safety (SCS)? Why are the ADSL demographic listings different (e.g., 372 rows for Study 303 in the ISS(Section 5.3.5.3) and 392 rows for 303 ISS (5.3.5.1))?

No, the datasets are not the same, because Module 5.3.5.1 includes 20 placebo subjects from Study 303 who did not enter the open-label lenvatinib treatment phase. This accounts for the numerical difference between Module 5.3.5.1 (N = 392) and Module 5.3.5.3 (N = 372).

5. Please explain in text form the following Analysis variable terms and what they mean (in plain English) from the Study 303 ISS analysis dataset with a cut off of March 2014 (Module 5.3.5.1). Also define the controlled terms that were used for each variable. The define file submitted in the application gives the statistical method of computation of the terms but it would be helpful to the clinical reviewer if you just explain what the terms refer to in text and not in statistical computational terms.

- EPOCH (and the definition of the terms in text)
- AETRTEM
- AEEMFL
- TRTEMFL
- TRT2EMFL
- APHASE
- SAFFL
- AESER
- SERCRITE

See attached MS Word File

6. Although not discussed during our telephone conference, since the define file for Study 303 ISS analysis dataset with a cut off of March 2014 (Module 5.3.5.1) lacks clarity in defining most variables, please submit a reviewer's guide or separate document that explains what the terms/variables are in text and not in statistical computational terms. This would facilitate our expedited review of the application. Please submit this document for the datasets ADSL,ADAE,ADEX,ADDS first (as soon as possible) and follow up with the rest of the analysis datasets (in 2-3 weeks).

Eisai plans to submit the requested document for the datasets, ADSL,ADAE,ADEX,ADDS by Wednesday, and will follow up with the remainder of the analysis datasets as soon as possible, but certainly with 2-3 weeks.

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

[attachment "emfinfo.txt" deleted by Susan Mayer/RIG/EisaiInc]

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/s/

DEANNE R VARNEY
10/23/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, October 21, 2014 8:05 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 - Pharmacovigilance IR

Hello Susan,

We have the following information request for NDA 206947. Please provide a response to me via email by COB on Wednesday, October 29th, and follow with a formal submission to your NDA.

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with lenvatinib following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the NDA application in the appropriate module so it can be reviewed accordingly.



FDA's Guidance on E2E
Pharmacovigilance Planning, 2005
FDA's Guidance on Good
Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, 2005

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

Guidance for Industry

E2E Pharmacovigilance Planning

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**April 2005
ICH**

Guidance for Industry

E2E Pharmacovigilance Planning

Additional copies are available from:

*Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>*

*Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
<http://www.fda.gov/cber/guidelines.htm>.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**April 2005
ICH**

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Guidance for Industry¹

E2E Pharmacovigilance Planning

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1, 1.1)²

This guidance is intended to aid in planning pharmacovigilance activities, especially in preparation for the early postmarketing period of a new drug (in this guidance, the term *drug* denotes chemical entities, biotechnology-derived products, and vaccines). The main focus of this guidance is on a safety specification and pharmacovigilance plan that might be submitted at the time of license application. The guidance can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the safety specification and pharmacovigilance plan into the Common Technical Document (CTD).

The guidance describes a method for summarizing the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied preapproval. It proposes a structure for a pharmacovigilance plan and sets out principles of good practice for the design and conduct of observational studies. It does not describe other methods to reduce risks from drugs, such as risk communication. The guidance takes into consideration ongoing work in the three regions and beyond on these issues.

¹ This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2004. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

² Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2004.

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This guidance does not cover the entire scope of pharmacovigilance. It uses the World Health Organization (WHO) definition of the term *pharmacovigilance* as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.” This definition encompasses the use of pharmacoepidemiological studies.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

A. Background (1.2)

The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed. In particular, during the early postmarketing period, the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a product is marketed, new information will be generated, which can have an impact on the benefits or risks of the product; evaluation of this information should be a continuing process, in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of medicines in a timely manner.

Industry and regulators have identified the need for better and earlier planning of pharmacovigilance activities before a product is approved or a license is granted. This ICH guidance has been developed to encourage harmonization and consistency and prevent duplication of effort and could be of benefit to public health programs throughout the world as they consider new drugs in their countries.

B. Scope of the Guidance (1.3)

The guidance could be most useful for new chemical entities, biotechnology-derived products, and vaccines, as well as for significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnology-derived product) and for established products that are to be introduced to new populations or in significant new indications or where a new major safety concern has arisen.

Contains Nonbinding Recommendations

The purpose of this guidance is to propose a structure for a pharmacovigilance plan and a safety specification that summarizes the identified and potential risks of the product to be addressed in the plan. The guidance is divided into the following sections:

- Safety specification
- Pharmacovigilance plan
- Annex — Pharmacovigilance Methods

It is recommended that company pharmacovigilance experts get involved early in product development. Planning and dialogue with regulators should also start long before license application. A safety specification and pharmacovigilance plan can also be developed for products already on the market (e.g., new indication or major new safety concern). The plan could be used as the basis for discussion of pharmacovigilance activities with regulators in the different ICH regions and beyond.

For products with important identified risks, important potential risks or important missing information, the pharmacovigilance plan should include additional actions designed to address these concerns. For products for which no special concerns have arisen, routine pharmacovigilance as described in section III.A.2 (3.1.2) of this guidance should be sufficient for postapproval safety monitoring, without the need for additional actions (e.g., safety studies).

During the course of implementing the various components of the plan, any important emerging benefit or risk information should be discussed and used to revise the plan.

The following principles underpin this guidance:

- Planning of pharmacovigilance activities throughout the product life-cycle
- Science-based approach to risk documentation
- Effective collaboration between regulators and industry
- Applicability of the pharmacovigilance plan across the three ICH regions

II. SAFETY SPECIFICATION (2)

The safety specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions that warrant further investigation to refine understanding of the benefit-risk profile during the postapproval period. This safety specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the pharmacovigilance plan. The safety specification can be built initially during the premarketing phase and, at the time approval is sought, it should reflect the status of issues that were being followed during development.

The Common Technical Document (CTD), especially the Overview of Safety (2.5.5), Benefits and Risks Conclusions (2.5.6), and the Summary of Clinical Safety (2.7.4) sections, includes information relating to the safety of the product and should be the basis of the safety issues identified in the safety specification. Sponsors should support the safety specification with

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references to specific pages of the CTD or other relevant documents. The safety specification can be a stand-alone document, usually in conjunction with the pharmacovigilance plan, but elements can also be incorporated into the CTD. The length of the document will generally depend on the product and its development program. Appendices can be added if it is considered important to provide a more detailed explanation of important risks or analyses.

A. Elements of the Safety Specification (2.1)

It is recommended that sponsors follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development program. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

The focus of the safety specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered for inclusion.

1. Nonclinical (2.1.1)

Within the Specification, this section should present nonclinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity, etc.)
- General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.)
- Drug interactions
- Other toxicity-related information or data

If the product is intended for use in special populations, consideration should be given to whether specific nonclinical data needs exist.

2. Clinical (2.1.2)

a. Limitations of the human safety database

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

The worldwide experience should be briefly discussed, including:

- The extent of the worldwide exposure
- Any new or different safety issues identified
- Any regulatory actions related to safety

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b. Populations not studied in the preapproval phase

The specification should discuss which populations have not been studied or have only been studied to a limited degree in the preapproval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed (CTD 2.5.5). Populations to be considered should include (but might not be limited to):

- Children
- The elderly
- Pregnant or lactating women
- Patients with relevant co-morbidity such as hepatic or renal disorders
- Patients with disease severity different from that studied in clinical trials
- Sub-populations carrying known and relevant genetic polymorphism
- Patients of different racial and/or ethnic origins

c. Adverse events (AEs)/adverse drug reactions (ADRs)

This section should list the important identified and potential risks that require further characterization or evaluation. Specific references should be made to guide a reviewer to where clinical safety data are presented (e.g., relevant sections of the CTD 2.5.5 and 2.7.4).

Discussion of risk factors and potential mechanisms that apply to identified AEs/ADRs should draw on information from any part of the CTD (nonclinical and clinical) and other relevant information, such as other drug labels, scientific literature, and postmarketing experience.

Identified risks for further evaluation

More detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These AEs/ADRs should usually call for further evaluation as part of the pharmacovigilance plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups).

Potential risks for further evaluation

Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterize the association.

d. Identified and potential interactions, including food-drug and drug-drug interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarized, and the potential health risks posed for the different indications and in the different populations should be discussed.

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e. Epidemiology

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed (because the epidemiology of the indication(s) may vary across regions), if this information is available.

In addition, for important adverse events that may require further investigation, it is useful to review the incidence rates of these events among patients in whom the drug is indicated (i.e., the background incidence rates). For example, if condition X is an important adverse event in patients who are treated with drug Y for disease Z, then it is useful to review the incidence of condition X in patients with disease Z who are not treated with drug Y; this is the background rate of condition X among patients with disease Z. Information on risk factors for an adverse event (condition X) would also be useful to include, if available.

f. Pharmacological class effects

The safety specification should identify risks believed to be common to the pharmacological class.

B. Summary (2.2)

At the end of the safety specification, a summary should be provided of the:

- Important identified risks
- Important potential risks
- Important missing information

Sponsors are encouraged to summarize specific ongoing safety issues on an issue-by-issue basis, including both nonclinical and clinical data that are pertinent to the problem.

III. PHARMACOVIGILANCE PLAN (3)

This section gives guidance on the structure of a pharmacovigilance plan. The pharmacovigilance plan should be based on the safety specification. The specification and plan can be written as two parts of the same document. The plan would normally be developed by the sponsor and can be discussed with regulators during product development, prior to approval (i.e., when the marketing application is submitted) of a new product, or when a safety concern arises postmarketing. It can be a stand-alone document, but elements could also be incorporated into the CTD.

For products for which no special concerns have arisen, routine pharmacovigilance as described in section III.A.2 (3.1.2) of this guidance should be sufficient for postapproval safety monitoring, without the need for additional actions (e.g., safety studies). However, for products with

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important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered.

The length of the document will likely depend on the product and its development program. The pharmacovigilance plan should be updated as important information on safety becomes available and milestones are reached.

A. Structure of the Pharmacovigilance Plan (3.1)

Outlined below is a suggested structure for the pharmacovigilance plan. The structure can be varied depending on the product in question and the issues identified in the safety specification.

1. Summary of Ongoing Safety Issues (3.1.1)

At the beginning of the pharmacovigilance plan, a summary should be provided of the:

- Important identified risks
- Important potential risks
- Important missing information

This is important if the pharmacovigilance plan is a separate document from the safety specification.

2. Routine Pharmacovigilance Practices (3.1.2)

Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a pharmacovigilance plan. This routine pharmacovigilance should include the following:

- Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner
- The preparation of reports for regulatory authorities:
 - Expedited adverse drug reaction (ADR) reports
 - Periodic safety update reports (PSURs)
- Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities
- Other requirements, as defined by local regulations

In some ICH regions, there might be a regulatory requirement to present within the pharmacovigilance plan an overview of the company's organization and practices for conducting pharmacovigilance. In the absence of such a requirement, a statement that the company's routine

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pharmacovigilance practices include the elements outlined in the bulleted list above should be sufficient.

3. Action Plan for Safety Issues (3.1.3)

The plan for each important safety issue should be presented and justified according to the following structure:

- Safety issue
- Objective of proposed action(s)
- Action(s) proposed
- Rationale for proposed action(s)
- Monitoring by the sponsor for safety issue and proposed action(s)
- Milestones for evaluation and reporting

Any protocols for specific studies can be provided in the CTD section 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., Module 4 if the study is a nonclinical study).

4. Summary of Actions To Be Completed, Including Milestones (3.1.4)

An overall pharmacovigilance plan for the product bringing together the actions for all individual safety issues should be presented. Whereas section 3.1.3 suggests presenting an action plan by ongoing safety issue, for this section the pharmacovigilance plan for the product should be organized in terms of the actions to be undertaken and their milestones. The reason for this is that one proposed action (e.g., a prospective safety cohort study) could address more than one of the identified issues.

It is recommended that milestones for completion of studies and other evaluations, and for submission of safety results, be included in the pharmacovigilance plan. In developing these milestones, one should consider when:

- Exposure to the product will have reached a level sufficient to allow potential identification/characterization of the AEs/ADRs of concern or resolution of a particular concern, and/or
- The results of ongoing or proposed safety studies are expected to be available.

These milestones might be aligned with regulatory milestones (e.g., PSURs, annual reassessment and license renewals) and used to revise the pharmacovigilance plan.

B. Pharmacovigilance Methods (3.2)

The best method to address a specific situation can vary, depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk, or missing information is the issue and whether signal detection, evaluation, or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, sponsors should employ the most

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appropriate design. The Annex provides a summary of the key methods used in pharmacovigilance. This is provided to aid sponsors considering possible methods to address specific issues identified by the safety specification. This list is not all-inclusive, and sponsors should use the most up-to-date methods that are relevant and applicable.

Design and Conduct of Observational Studies (3.2.1)

Carefully designed and conducted pharmacoepidemiological studies, specifically observational (noninterventional, nonexperimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator “observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice.”¹

Before the observational study that is part of a pharmacovigilance plan commences, a protocol should be finalized. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the pharmacovigilance plan.

Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator’s interpretation of the findings.

It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology.² In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed.

The highest possible standards of professional conduct and confidentiality should always be maintained, and any relevant national legislation on data protection followed.

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IV. REFERENCES (4)

1. CIOMS, Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. Geneva; World Health Organization (WHO), 2001.
2. Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, http://www.pharmacoepi.org/resources/guidelines_08027.cfm, August 2004.

ANNEX — PHARMACOVIGILANCE METHODS

1. Passive Surveillance

- **Spontaneous Reports**

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g., WHO, regional centers, poison control center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.¹

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other premarketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug.^{2,3,4,5}

Systematic Methods for the Evaluation of Spontaneous Reports

More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection.^{6,7,8} Data mining techniques have also been used to examine drug-drug interactions.⁹ Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

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- **Case Series**

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome.^{10, 11} Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

2. Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods.¹² Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a predesigned method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early postmarketing phase, companies might actively provide health professionals with safety information, and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early postmarketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan). This should be regarded as a form of spontaneous event reporting; thus, data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

3. Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous preorganized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact.¹³ In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

- **Sentinel Sites**

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting

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system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites¹⁴. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysis centers, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

- **Drug Event Monitoring**

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at prespecified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.^{12, 15, 16, 17} Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

- **Registries**

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

Exposure (drug) registries address populations exposed to drugs of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

4. Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective).^{12, 15}

- **Cross-sectional Study (Survey)**

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

- **Case-control Study**

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction, that might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

- **Cohort Study**

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but nonexposed at another time point. Since the population exposure during follow-up

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is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes. Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

There are several automated databases available for pharmacoepidemiologic studies.^{12, 15, 18} They include databases that contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets might include millions of patients. Since they are created for administrative or billing purposes, they might not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

5. Targeted Clinical Investigations

When significant risks are identified from preapproval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from preapproval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the event of interest will be

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focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. Large, simplified trials are also resource-intensive.

6. Descriptive Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

- **Natural History of Disease**

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective.¹⁵ For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

- **Drug Utilization Study**

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes.¹² These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

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Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**March 2005
Clinical Medical**

Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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**U.S. Department of Health and Human Services
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Guidance for Industry¹

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

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I. INTRODUCTION

This document provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components).² Specifically, this document provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

¹ This guidance has been prepared by the PDUFA III Pharmacovigilance Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² For ease of reference, this guidance uses the term *product* or *drug* to refer to all products (excluding blood and blood components) regulated by CDER and CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.

Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0001 (until March 31, 2005) and 0910-0338 (until August 31, 2005).

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A. PDUFA III's Risk Management Guidance Goal

On June 12, 2002, Congress reauthorized, for the second time, the Prescription Drug User Fee Act (PDUFA III). In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting premarketing risk assessment, (2) developing and implementing risk minimization tools, and (3) performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9 – 11, 2003, to discuss the concept papers. FDA considered all of the comments received in developing three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

1. *Premarketing Risk Assessment (Premarketing Guidance)*
2. *Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)*
3. *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)*

B. Overview of the Risk Management Guidances

Like the concept papers and draft guidances that preceded them, each of the three final guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on premarketing and postmarketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

- Many recommendations in this guidance are ***not*** intended to be generally applicable to all products.

Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (see e.g., FDA requirements for professional labeling, and adverse

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event monitoring and reporting). As a result, many of the recommendations presented here focus on situations when a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for all products or only this subset of products.

- It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy.³

- To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as appropriate.

The topics covered in this guidance are being discussed in a variety of international forums. We are participating in these discussions and believe that, to the extent possible, the recommendations in this guidance reflect current thinking on related issues.

- When planning risk assessment and risk minimization activities, sponsors should consider input from health care participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and third party payers).
- There are points of overlap among the three guidances.

We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

III. THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

³ See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to FDA (45 CFR 164.512(b)(1)(i) and (iii), and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see <http://www.hhs.gov/ocr/hipaa>.

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This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term *pharmacovigilance* to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.

Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

A. Good Reporting Practice

Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events,⁴ and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer, it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

⁴ Good reporting practices are extensively addressed in a proposed FDA regulation and guidance documents. See (1) Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, 68 FR 12406 (March 14, 2003), (2) FDA guidance for industry on *Postmarketing Reporting of Adverse Experiences*, (3) FDA guidance for industry on *E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR)*, (4) FDA guidance for industry on *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

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FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

B. Characteristics of a Good Case Report

Good case reports include the following elements:

1. Description of the adverse events or disease experience, including time to onset of signs or symptoms;
2. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;
3. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;
4. Documentation of the diagnosis of the events, including methods used to make the diagnosis;
5. Clinical course of the event and patient outcomes (e.g., hospitalization or death);⁵
6. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;
7. Information about response to dechallenge and rechallenge; and
8. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, good case reports also include full descriptions of the following, when such information is available:

1. Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container);
2. Sequence of events leading up to the error;
3. Work environment in which the error occurred; and
4. Types of personnel involved with the error, type(s) of error, and contributing factors.

⁵ Patient outcomes may not be available at the time of initial reporting. In these cases, follow-up reports can convey important information about the course of the event and serious outcomes, such as hospitalization or death.

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FDA recommends that sponsors capture in the case narrative section of a medication error report all appropriate information outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy.⁶ Although sponsors are not required to use the taxonomy, FDA has found the taxonomy to be a useful tool to categorize and analyze reports of medication errors. It provides a standard language and structure for medication error-related data collected through reports.

C. Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS) or Vaccine Adverse Events Reporting System (VAERS), using thorough database search strategies based on updated coding terminology (e.g., the Medical Dictionary for Regulatory Activities (MedDRA)). When available, FDA recommends that standardized case definitions (i.e., formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series.⁷ In general, FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation (see section IV.F. for more details).

As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

1. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);
2. Absence of symptoms related to the event prior to exposure;
3. Evidence of positive dechallenge or positive rechallenge;
4. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;
5. Consistency of the event with the known effects of other products in the class;

⁶ See <http://www.nccmerp.org> for the definition of a medication error and taxonomy of medication errors.

⁷ See, for example, Institute of Medicine (IOM) Immunization Safety Review on Vaccines and Autism, 2004.

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6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and
7. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA does not recommend any specific categorization of causality, but the categories *probable*, *possible*, or *unlikely* have been used previously.⁸ If a causality assessment is undertaken, FDA suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. A number of references are available to assist sponsors in capturing a complete account of the event.⁹ FDA recommends that sponsors follow up to the extent possible with reporters to capture a complete account of the event, focusing on the *medication use systems* (e.g., prescribing/order process, dispensing process, administration process). This data may be informative in developing strategies to minimize future errors.

D. Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

1. The clinical and laboratory manifestations and course of the event;

⁸ See World Health Organization, the Uppsala Monitoring Center, 2000, *Safety Monitoring of Medicinal Product*, for additional categorizations of causality.

⁹ See Cohen MR (ed), 1999, *Medication Errors*, American Pharmaceutical Association, Washington DC; Cousins DD (ed), 1998, *Medication Use: A Systems Approach to Reducing Errors*, Joint Commission on Accreditation of Healthcare Organizations, Oakbrook Terrace, IL.

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2. Demographic characteristics of patients with events (e.g., age, gender, race);
3. Exposure duration;
4. Time from initiation of product exposure to the adverse event;
5. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;
6. Use of concomitant medications;
7. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;
8. The route of administration (e.g., oral vs. parenteral);
9. Lot numbers, if available, for products used in patients with events; and
10. Changes in event reporting rate over calendar time or product life cycle.

E. Use of Data Mining to Identify Product-Event Combinations

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or so-called *data mining*, can provide additional information about the existence of an excess of adverse events reported for a product. By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product-event combinations warranting further investigation. Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the "observed reporting fraction") with (2) the fraction of reports for the same particular event for all drugs (i.e., "the expected reporting fraction").¹⁰ This analysis can be refined by adjusting for aspects of reporting (e.g., the reporting year) or characteristics of the patient (e.g., age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease.

The score (or statistic) generated by data mining quantifies the disproportionality between the observed and expected values for a given product-event combination. This score is compared to a threshold that is chosen by the analyst. A potential excess of adverse events is operationally defined as any product-event combination with a score exceeding the specified threshold. When

¹⁰ Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

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applying data mining to large databases (such as AERS), it is not unusual for a product to have several product-event combinations with scores above a specified threshold. The lower the threshold, the greater the likelihood that more combinations will exceed the threshold and will warrant further investigation.

Several data mining methods have been described and may be worth considering, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm^{11,12}, the Proportional Reporting Ratio (PRR) method^{13,14} and the Neural Network approach.¹⁵ Except when the observed number of cases with the drug event combination is small (e.g., less than 20) or the expected number of cases with the drug event combination is < 1 , the MGPS and PRR methods will generally identify similar drug event combinations for further investigation.¹⁶

Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products. FDA exercises caution when making such comparisons, because voluntary adverse event reporting systems such as AERS or VAERS are subject to a variety of reporting biases (e.g., some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other comorbidities or unrecorded confounders, may cause the events to be reported). In addition, AERS or VAERS data may be affected by the submission of incomplete or duplicate reports, under-reporting, or reporting stimulated by publicity or litigation. As reporting biases may differ by product and change over time, and could change differently for different events, it is not possible to predict their impact on data mining scores.

Use of data mining techniques is not a required part of signal identification or evaluation. If data mining results are submitted to FDA, they should be presented in the larger appropriate clinical epidemiological context. This should include (1) a description of the database used, (2) a description of the data mining tool used (e.g., statistical algorithm, and the drugs, events and

¹¹ DuMouchel W and Pregibon D, 2001, Empirical Bayes screening for multi-item associations, *Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining*.

¹² Szarfman A, Machado SG, and O'Neill RT, 2002, Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database, *Drug Safety* 25(6): 381-92.

¹³ Evans SJW, Waller P, and Davis S, 1998, Proportional reporting ratios: the uses of epidemiological methods for signal generation [abstract], *Pharmacoepidemiology and Drug Safety* 7:S102.

¹⁴ Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

¹⁵ Bate A et al., 1998, A Bayesian neural network method for adverse drug reaction signal generation, *European Journal of Clinical Pharmacology* 54:315-21.

¹⁶ This conclusion is based on the experience of FDA and of William DuMouchel, Ph.D., Chief Scientist, Lincoln Technologies, Wellsley, MA, as summarized in an email communication from Dr. DuMouchel to Ana Szarfman, M.D., Ph.D., Medical Officer, OPaSS, CDER, on October 13, 2004.

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stratifications selected for the analyses) or an appropriate reference, and (3) a careful assessment of individual case reports and any other relevant safety information related to the particular drug-event combination of interest (e.g., results from preclinical, clinical, pharmacoepidemiologic, or other available studies).

F. Safety Signals That May Warrant Further Investigation

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, numbers treated, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

1. New unlabeled adverse events, especially if serious;
2. An apparent increase in the severity of a labeled event;
3. Occurrence of serious events thought to be extremely rare in the general population;
4. New product-product, product-device, product-food, or product-dietary supplement interactions;
5. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);
6. Confusion about a product's name, labeling, packaging, or use;
7. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);
8. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal);¹⁷ and
9. Other concerns identified by the sponsor or FDA.

G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment.

¹⁷ For a detailed discussion of risk minimization action plan evaluation, please consult the *RiskMAP Guidance*.

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In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate. Limitations in national denominator estimates arise because:

1. Accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available;
2. It may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low;¹⁸ and
3. A product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator.^{19,20} FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes.

To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). These background rates can be derived from: (1) national health statistics, (2) published medical literature, or (3) ad hoc studies, particularly of

¹⁸ See *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group V, Geneva, 2001.

¹⁹ See Rodriguez EM, Staffa JA, Graham DJ, 2001, *The role of databases in drug postmarketing surveillance*, *Pharmacoepidemiology and Drug Safety*, 10:407-10.

²⁰ In addition to U.S. reporting rates, sponsors can provide global reporting rates, when relevant.

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subpopulations, using large automated databases or ongoing epidemiologic investigations with primary data collection. FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria, and duration of time at risk.

While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g., publicity, newness of product to the market) and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

V. BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES

FDA recognizes that there are a variety of methods for investigating a safety signal. Signals warranting additional investigation can be further evaluated through carefully designed non-randomized observational studies of the product's use in the "real world" and randomized trials. The *Premarketing Guidance* discusses a number of types of randomized trials, including the large simple safety study, which is a risk assessment method that could be used either pre- or post-approval.

This document focuses on three types of non-randomized observational studies: (1) pharmacoepidemiologic studies, (2) registries, and (3) surveys. By focusing this guidance on certain risk assessment methods, we do not intend to advocate the use of these approaches over others. FDA encourages sponsors to consider all methods to evaluate a particular safety signal. FDA recommends that sponsors choose the method best suited to the particular signal and research question of interest. Sponsors planning to evaluate a safety signal are encouraged to communicate with FDA as their plans progress.

A. Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-crossover, or other models.²¹ The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests prespecified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse

²¹ *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004 (http://www.pharmacoepi.org/resources/guidelines_08027.cfm)

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event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the premarketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated prior to marketing (e.g., to study the natural history of disease or patterns of product use, or to estimate background rates for adverse events).

For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power. Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000 (an exception may be larger trials conducted for some vaccines, which could move the threshold to 1:10,000). It may also be difficult to use clinical trials: (1) to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications, or (2) to identify certain risk factors for a particular adverse event. On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials may be preferable to observational studies.

Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high.

Because different products pose different benefit-risk considerations (e.g., seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be made on a case-by-case basis. When an important adverse event–product association leads to questions on the product’s benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest.

When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding. Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study.²² Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different designs. Agreement of the results from more than one study helps to provide reassurance that the observed results are robust.

²² See, for example, Strom BL (ed), 2000, *Pharmacoepidemiology*, 3rd edition, Chichester: John Wiley and Sons, Ltd; Hartzema AG, Porta M, and Tilson HH (eds), 1998, *Pharmacoepidemiology: An Introduction*, 3rd edition, Cincinnati, OH: Harvey Whitney Books.

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There are a number of references describing methodologies for pharmacoepidemiologic studies, discussing their strengths and limitations,²³ and providing guidelines to facilitate the conduct, interpretation, and documentation of such studies.²⁴ Consequently, this guidance document does not comprehensively address these topics. However, a protocol for a pharmacoepidemiologic study generally includes:

1. Clearly specified study objectives;
2. A critical review of the literature; and
3. A detailed description of the research methods, including:
 - the population to be studied;
 - the case definitions to be used;
 - the data sources to be used (including a rationale for data sources if from outside the U.S.);
 - the projected study size and statistical power calculations; and
 - the methods for data collection, management, and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such as data from previously conducted clinical trials or large databases. In recent years, a number of pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO, Medicaid) that allow retrieval of records on product exposure and patient outcomes. In addition, recently, comprehensive electronic medical record databases have also been used for studying drug safety issues. Depending on study objectives, factors that may affect the choice of databases include the following:

1. Demographic characteristics of patients enrolled in the health plans (e.g., age, geographic location);
2. Turnover rate of patients in the health plans;
3. Plan coverage of the medications of interest;
4. Size and characteristics of the exposed population available for study;
5. Availability of the outcomes of interest;
6. Ability to identify conditions of interest using standard medical coding systems (e.g., International Classification of Diseases (ICD-9)), procedure codes or prescriptions that could be used as markers;

²³ Ibid.

²⁴ *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004 (http://www.pharmacoepi.org/resources/guidelines_08027.cfm).

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7. Access to medical records; and
8. Access to patients for data not captured electronically.

For most pharmacoepidemiologic studies, FDA recommends that sponsors validate diagnostic findings through a detailed review of at least a sample of medical records. If the validation of the specific outcome or exposure of interest using the proposed database has been previously reported, FDA recommends that the literature supporting the validity of the proposed study be submitted for review.

FDA encourages sponsors to communicate with the Agency when pharmacoepidemiologic studies are being developed.

B. Registries

The term *registry* as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects.”²⁵ Whenever possible, a control or comparison group should be included, (i.e., individuals with a disease or risk factor who are not treated or are exposed to medical interventions other than the intervention of interest).²⁶

Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics.²⁷

Registries can be particularly useful for:

1. Collecting outcome information not available in large automated databases; and
2. Collecting information from multiple sources (e.g., physician records, hospital summaries, pathology reports, vital statistics), particularly when patients receive care from multiple providers over time.

A sponsor can initiate a registry at any time. It may be appropriate to initiate the registry at or before initial marketing, when a new indication is approved, or when there is a need to evaluate

²⁵ See Frequently Asked Questions About Medical and Public Health Registries, The National Committee on Vital and Health Statistics, at <http://www.ncvhs.hhs.gov>.

²⁶ See for example, FDA Guidance for Industry, *Establishing Pregnancy Exposure Registries*, August 2002 <http://www.fda.gov/cder/guidance/3626fnl.pdf>.

²⁷ Ibid.

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safety signals identified from spontaneous case reports. In deciding whether to establish a registry, FDA recommends that a sponsor consider the following factors:

1. The types of additional risk information desired;
2. The attainability of that information through other methods; and
3. The feasibility of establishing the registry.

Sponsors electing to initiate a registry should develop written protocols that provide: (1) objectives for the registry, (2) a review of the literature, and (3) a summary of relevant animal and human data. FDA suggests that protocols also contain detailed descriptions of: (1) plans for systematic patient recruitment and follow-up, (2) methods for data collection, management, and analysis, and (3) conditions under which the registry will be terminated. A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity, and validation of registry findings against a sample of medical records or through interviews with health care providers. FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study and we encourage sponsors to discuss their registry development plans with FDA.

C. Surveys

Patient or health care provider surveys can gather information to assess, for example:

1. A safety signal;
2. Knowledge about labeled adverse events;
3. Use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist;
4. Compliance with the elements of a RiskMAP (e.g., whether or not a Medication Guide was provided at the time of product dispensing); and²⁸
5. Confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names.

Like a registry, a survey can be initiated by a sponsor at any time. It can be conducted at the time of initial marketing (i.e., to fulfill a postmarketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

FDA suggests that sponsors electing to initiate a survey develop a written protocol that provides objectives for the survey and a detailed description of the research methods, including: (1) patient or provider recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management, and analysis.²⁹ FDA recommends that a survey-based monitoring

²⁸ For a detailed discussion of RiskMAP evaluation, please consult the *RiskMAP Guidance*.

²⁹ See 21 CFR parts 50 and 56 for FDA's regulations governing the protection of human subjects.

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system include carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers, whenever possible. FDA recommends that survey instruments be validated or piloted before implementation. FDA suggests that sponsors consider whether survey translation and cultural validation would be important.

Sponsors are encouraged to discuss their survey development plans with FDA.

VI. INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK

After identifying a safety signal, FDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also: (1) employ data mining techniques, and (2) calculate reporting rates for comparison to background rates. Based on these findings and other available data (e.g., from preclinical or other sources), FDA suggests that a sponsor consider further study (e.g., observational studies) to establish whether or not a potential safety risk exists.

When evaluation of a safety signal suggests that it may represent a potential safety risk, FDA recommends that a sponsor submit a synthesis of all available safety information and analyses performed, ranging from preclinical findings to current observations. This submission should include the following:

1. Spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;
2. Background rate for the event in general and specific patient populations, if available;
3. Relative risks, odds ratios, or other measures of association derived from pharmacoepidemiologic studies;
4. Biologic effects observed in preclinical studies and pharmacokinetic or pharmacodynamic effects;
5. Safety findings from controlled clinical trials; and
6. General marketing experience with similar products in the class.

After the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event. FDA suggests that the sponsor's submission provide an assessment of the benefit-risk balance of the product for the population of users as a whole and for identified at-risk patient populations, and, if appropriate, (1) propose steps to further investigate the signal through additional studies, and (2) propose risk

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minimization actions.³⁰ FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class) and will communicate its conclusions to the sponsor whenever possible. Factors that are typically considered include:

1. Strength of the association (e.g., relative risk of the adverse event associated with the product);
2. Temporal relationship of product use and the event;
3. Consistency of findings across available data sources;
4. Evidence of a dose-response for the effect;
5. Biologic plausibility;
6. Seriousness of the event relative to the disease being treated;
7. Potential to mitigate the risk in the population;
8. Feasibility of further study using observational or controlled clinical study designs; and
9. Degree of benefit the product provides, including availability of other therapies.

As noted in section II, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps.³¹ FDA recommends that assessment of causality and of strategies to minimize product risk occur on an ongoing basis, taking into account the findings from newly completed studies.

VII. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket requirements under the FDCA and FDA implementing regulations) is sufficient for postmarketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A

³⁰ In the vast majority of cases, risk communication that incorporates appropriate language into the product's labeling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a RiskMAP. Please refer to the *RiskMAP Guidance* for a complete discussion of RiskMAP development.

³¹ For additional discussion of the relationship between risk assessment and risk minimization, please consult the *RiskMAP Guidance*.

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pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.³² The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. The likelihood that the adverse event represents a potential safety risk;
2. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);
3. The severity of the event;
4. The nature of the population(s) at risk;
5. The range of patients for which the product is indicated (broad range or selected populations only); and
6. The method by which the product is dispensed (through pharmacies or performance linked systems only).³³

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (RiskMAP), as described in the *RiskMAP Guidance*. Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product's pharmacovigilance plan.

FDA believes that for a product without safety risks identified pre- or post-approval and for which at-risk populations are thought to have been adequately studied, routine spontaneous reporting will be sufficient for postmarketing surveillance. On the other hand, pharmacovigilance plans may be appropriate for products for which: (1) serious safety risks have been identified pre- or post-approval, or (2) at-risk populations have not been adequately studied.

³² As used in this document, the term "pharmacovigilance plan" is defined differently than in the ICH draft E2E document (version 4.1). As used in the ICH document, a "pharmacovigilance plan" would be routinely developed (i.e., even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks. This ICH guidance is available on the Internet at <http://www.fda.gov/cder/guidance/index.htm> under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November, 2004.

³³ For a detailed discussion of controlled access systems, please consult the *RiskMAP Guidance*.

Contains Nonbinding Recommendations

Sponsors may discuss with the Agency the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

1. Submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e., as 15-day reports);
2. Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually);
3. Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be (1) drug based: identifying adverse events in patients taking certain products, (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or (3) event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure);
4. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs (see section V);
5. Creation of registries or implementation of patient or health care provider surveys (see section V); and
6. Additional controlled clinical trials.³⁴

As data emerges, FDA recommends that a sponsor re-evaluate the safety risk and the effectiveness of its pharmacovigilance plan. Such re-evaluation may result in revisions to the pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions on potential safety risks and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee or the FDA Advisory Committee dealing with the specific product in question. Such committees may be convened when FDA seeks: (1) general advice on the design of pharmacoepidemiologic studies, (2) comment on specific pharmacoepidemiology studies developed by sponsors or FDA for a specific product and safety question, or (3) advice on the interpretation of early signals from a case series and on the need for further investigation in pharmacoepidemiologic studies. While additional information is being developed, sponsors working with FDA can take interim actions to communicate information about potential safety risks (e.g., through labeling) to minimize the risk to users of the product.

³⁴ For a discussion of risk assessment in controlled clinical trials, please consult the *Premarketing Guidance*.

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/s/

DEANNE R VARNEY
10/21/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, October 21, 2014 3:48 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 Information Request

Hello Susan,

We have the following information request for NDA 206947. Please provide a response to me via email by COB on Thursday, October 23rd, and follow with a formal amendment to your NDA.

Reference is made to your slide 56 of the Application Orientation Meeting slide deck which states, "PFS (and PR or dSD for ≥ 23 wks) significantly increased with increased lenvatinib exposure (AUC_{0-24,ss} and C_{max,ss})". Please direct us to the study reports where the details of the exposure-response analysis can be obtained.

Please confirm receipt.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
10/21/2014

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, October 15, 2014 2:29 PM
To: Susan_Mayer@eisai.com
Subject: Lenvatinib NDA 206947 - Clinical Information Request

Hello Susan,

In follow-up to the teleconference this morning with the clinical team, please provide responses for the following issues discussed during the teleconference to me via email, and follow with a formal amendment to your NDA:

1. The MedDRA version that was used for AE coding for the different datasets and the CTCAE toxicity grading scale for adverse event and laboratory values grading.
2. The contents of the Errata for the CSR for Study 303 and confirmation as to whether any of it changes the ultimate risk benefit profile (or information contained in product labeling) of lenvatinib for the proposed indication.

Additionally, please provide a response to the following clinical requests and clarifications as soon as possible to me via email, and follow with a formal amendment to your NDA:

3. Please explain the following statement in page 11 of the Analysis Data Reviewers guide for Study 303 Mar 15, 2014 cut off Module 5.3.5.1 : "For patients with Placebo in period 1 and Lenvatinib in Period 02 (Open Label), the data in period 02 are pooled in the analysis".
4. Are the datasets used for the safety progress report for Study 303 with a March 15, 2014 cut-off the same as those that generated the summary of clinical safety (SCS)? Why are the ADSL demographic listings different (e.g., 372 rows for Study 303 in the ISS(Section 5.3.5.3) and 392 rows for 303 ISS (5.3.5.1))?
5. Please explain in text form the following Analysis variable terms and what they mean (in plain English) from the Study 303 ISS analysis dataset with a cut off of March 2014 (Module 5.3.5.1). Also define the controlled terms that were used for each variable. The define file submitted in the application gives the statistical method of computation of the terms but it would be helpful to the clinical reviewer if you just explain what the terms refer to in text and not in statistical computational terms.
 - EPOCH (and the definition of the terms in text)
 - AETRTEM
 - AEEMFL
 - TRTEMFL
 - TRT2EMFL
 - APHASE
 - SAFFL
 - AESER
 - SERCRITE
6. Although not discussed during our telephone conference, since the define file for Study 303 ISS analysis dataset with a cut off of March 2014 (Module 5.3.5.1) lacks clarity in defining most variables, please submit a reviewer's guide or separate document that explains what the terms/variables are in text and not in statistical computational terms. This

would facilitate our expedited review of the application. Please submit this document for the datasets ADSL,ADAE,ADEX,ADDS first (as soon as possible) and follow up with the rest of the analysis datasets (in 2-3 weeks).

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
10/15/2014



NDA 206947

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Eisai, Inc.
Attention: Susan Mayer
Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) dated August 14, 2014, received August 14, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for lenvatinib capsules, 4 mg and 10 mg.

We also refer to your amendments dated September 4, 8, 10, and 16, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm> . Therefore, the user fee goal date is **April, 14, 2015**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 16, 2015. In addition, the planned date for our internal mid-cycle review meeting is November 4, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

Clinical:

1. Address the following issues in the study data tabulation model (SDTM) datasets for Study 303:
 - a. Identify the dataset “xm” which is missing from the define file of the SDTM datasets.
 - b. Explain the use of the term “heart rate” labeled as “pulse rate” in the VS domain. Please note that this represents a non-standard value.
 - c. Identify the missing values for standardized lab result units and list the laboratory values for which units are missing.
 - d. Provide a list of the laboratory tests listed in non-controlled terminology, e.g., “alkaline phosphatase 315-PNL.”
 - e. Provide a narrative for all patients coded as DSDECOD “other” in the DS dataset who have a DSTERM of “clinical progression.”
2. Listings datasets provided in Module 5.3.5 are empty. Please provide an explanation or updated datasets if appropriate. Additionally, provide a reviewers guide to these datasets as appropriate.

Biopharmaceutics:

3. The dissolution stability data are currently reported at only the proposed specification-sampling time point of ^{(b) (4)} minutes. Please submit, in SAS transport file format, the complete multi-point dissolution profiles obtained in the stability program for every batch, under all storage conditions and packaging configurations. If multiple time point profiling data were not collected, perform a full profiling (n=12) of the registration and clinical batches at the current stability time point using the following sampling times: 10, 15, 20, and 30 minutes and submit these data to the NDA. Thereafter, continue with the full dissolution profiling for the remainder of the stability program.
4. The experimental data in support of your proposed dissolution method’s suitability for your product is missing from the NDA. Submit the dissolution method development report supporting the selection of the proposed dissolution test. Include in the report the developmental parameters (i.e., rationale for selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, surfactant type and amount, assay, sink conditions, etc.) that support the proposed dissolution method as optimal for your product. Your proposed dissolution acceptance criterion should be based on the complete dissolution profile data (n=12) for all pivotal clinical and primary stability/registration

batches. For your immediate release product, the selection of the specification time point should be where $Q = \frac{(b)}{(4)}$ % dissolution occurs.

Microbiology:

5. You propose to perform (b) (4)
- However, microbial limits testing may be omitted from the product release specification provided adequate upstream microbiological controls are established and documented. If you wish to omit the microbial limits specification, more information on your process is needed. Address the following points:
- a. Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product. This should include the maximum processing time for the (b) (4) step.
 - b. If applicable, describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.
 - c. Describe activities taken when microbiological acceptance criteria are not met at control points.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specifications. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.

Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

6. Add a horizontal line to separate the Table of Contents (TOC) from the Full Prescribing Information (FPI).
7. Delete the white space between the Highlights Heading and the Highlights Limitation Statement.
8. Include the following **bolded** heading in upper case at the beginning of the FPI: **“FULL PRESCRIBING INFORMATION”**
9. Section 17 of the package insert currently states (b) (4)
We recommend that you revise this to state “Advise the patient to read the FDA-approved patient-labeling (Patient Information).”
10. Delete (b) (4)

We have also identified several labeling content issues. These issues are described using the track changes “comment” function within the text of your PI, and are included as an attachment to this letter. Please review all content issues and revise your PI accordingly.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 31, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information within 30 days of the date of this letter. While we anticipate that any response submitted in a timely manner will be reviewed during this

review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Deanne Varney, Senior Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

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

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

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/s/

PATRICIA KEEGAN
10/10/2014

FILING MEETING MINUTES

September 25, 2014

New NDA 206947
Lenvatinib
Eisai

Submission Date: August 14, 2014
Received Date: August 14, 2014
PDUFA Date: April 14, 2015

Proposed Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Core Review Team:

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Gaetan Ladouceur, CMC
Amit Mitra, CMC
Liang Zhou, CMC Team Leader
Ali Al Hakim, CMC (Branch Chief)
Teicher Agosto, CMC (ONDQA RPM)
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader
Okpo Eradiri, Biopharmaceutics Reviewer
Angelica Dorantes, Biopharmaceutics Team Leader
Jessica Cole, Quality Microbiology Reviewer

Consults:

Nick Senior, OPDP / Jessica Cleck Dereneck, OPDP TL
Nathan Caulk, PLT / Barbara Fuller, PLT TL
Afrouz Nayernama, DPV / Tracy Salaam, DPV TL
Carolyn Yancy, DRISK / Doris Auth, DRISK TL
Otto Townsend, DMEPA / Alice Tu, DMEPA TL
Hui-Lee Wong, DEPI / Steven Bird, DEPI TL / Kate Gelperin, DEPI Acting TL
Lauren Iacono-Connors, OSI / Janice Pohlman, OSI TL
Miriam Dinatale, PMHS / Jeanine Best, TL / Alyson Karesh, Acting TL / Vicki Moyer, PM

Agenda Items:

1. Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
 - Confirm Priority Review
 - **Discussion:** If proceed with priority review based on the small subpopulation that received prior VEGF therapy, might need to identify the subpopulation in the label. Would be best not to identify this in the label; therefore, cannot rely too heavily on this as a basis for a priority review.
 - **Final Decision:** Will be determined by September 30th, after review of response rate data.
 - **Post-Meeting Addendum:** Priority review will be granted.
- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of lenvatinib has been conducted under INDs (b)(4) and 113656

2. Milestone Dates for 8-Month Priority Review Clock:

Milestone	8 month review
Acknowledgment Letter	August 28, 2014 <i>Issued August 28, 2014</i>
Priority Review Determination OR Filing Issues Identified/Not Identified Letter	October 13, 2014
Filing Issues Identified (74 Day Letter) --- if not sent in Day 60 letter	October 27, 2014
Mid-Cycle Meeting	Month 3 – November 12, 2014
Mid-Cycle Communication	Month 3.5 – November 27, 2014
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 – January 16, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Month 5.25 (~mid-January)
Late Cycle Meeting Target Date	Month 6 if no AC (~mid-February)
Advisory Committee Target Date	Month 6 – February 12, 2015
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 – January 14, 2015 Month 5.1 – January 17, 2015 Month 7 – March 19, 2015 1.5 weeks pre-action – April 3, 2015 April 14, 2015
Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action – March 10, 2015
Compile and circulate Action Letter and Action Package	3 weeks pre-action – March 24, 2015
FINAL Action Letter Due	April 14, 2015

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3. Filing Issues:

- a. **Clinical:** Application is filable. Comment regarding SDTM datasets for inclusion is 74-day letter. Consult request for statistics safety group might be required.
- b. **Statistics:** Application is filable. No comments for 74-day letter
- c. **Clinical Pharmacology:** Application is filable. No comments for 74-day letter
- d. **Pharmacometrics:** Application is filable. No comments for 74-day letter
- e. **Genomics:** Application is filable. No comments for 74-day letter
- f. **Nonclinical:** Application is filable. No comments for 74-day letter
- g. **CMC:** Application is filable. No comments for 74-day letter
- h. **Biopharmaceutics:** Application is fillable. Two comments for inclusion in 74-day letter.
- i. **Microbiology:** Application is filable. One comment for inclusion in 74-day letter
- j. **Regulatory:** Application is filable. Labeling comments will be included in 74-day letter

4. Inspections:

- a. **Clinical Site Inspections:** All clinical inspection assignments have been issued, and OSI should be able to comply with a mid-January 2015 due date.
- b. **Manufacturing Site Inspections:** Compliance has no issues with the application and inspections are being scheduled at this time. Not currently aware if any sites have no inspectional history.

5. Internal Team Meetings:

Discussion: Labeling meetings will remain scheduled for December and January regardless of review timeline. A decision will be made regarding the midcycle after the review priority determination is made.

- **Mid-Cycle Meeting:** November 4, 2014
 - **Mid-Cycle Communication Sponsor Tcon:** Tentatively scheduled for November 19, 2014
 - **Labeling Meetings** (suggested section groupings):
 - a. December 1, 2014: CMC and Nonclinical - Sections 3, 11, 13, 16
 - b. December 2, 2014: Clin Pharm and Clinical – Sections 2, 4, 7, 8, 10, 12
 - c. December 8, 2014: Clinical and Statistics – Sections 1, 5, 6
 - d. December 10, 2014: Clinical and Statistics – Sections 14 and 17
 - e. December 17, 2014: Highlights and Remaining Issues
 - f. January 12, 2015: If needed
 - **Monthly Team Meetings:**
 - a. October 23, 2014
 - b. November 19, 2014
 - c. December 17, 2014
 - d. January 21, 2015
 - e. February 16, 2015
 - f. March 19, 2015
 - g. April 6, 2015
 - **Late Cycle Meeting:** TBD, By mid-February
 - **Wrap- Up Meeting:** TBD, By March 10, 2015.
6. **Applicant Orientation Presentation:** Scheduled for September 26, 2014.
- Discussion:** Core team will attend in person. Will ask Eisai about the inspectional history of all manufacturing facilities.
7. **ODAC: Not Required**
8. **SGE's:** An SGE and patient representative will be required.

Proposed SGE's:
Antonio Fojo

Michael Menefee

Proposed Patient Representative:

(b) (4)

Discussion: No discussion occurred.

8. Additional Items or Issues: None

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/s/

DEANNE R VARNEY
10/07/2014

Varney, Deanne

From: Varney, Deanne
Sent: Friday, August 29, 2014 11:41 AM
To: Susan_Mayer@eisai.com
Subject: NDA 206947 - Clinical Information Request

Hello Susan,

Please provide the following information to me via email by COB on Tuesday, September 2nd, and follow with an amendment to your NDA.

Please provide the address for the location of all records and source documents for the IRR, as well as a point of contact (name, phone number, and email address).

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
09/03/2014

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, September 02, 2014 11:04 AM
To: Susan_Mayer@eisai.com
Subject: NDA 206947 - Information Request

Hello Susan,

We have the following information request in addition to the Clinical Pharmacology and Cardiac Safety Table.

After reviewing the clinical datasets of Study E7080-A001-002, we found the following data quality issues in EG.XPT:

- 1) *Identical EGDTC, EGTPT but different interval measurements, see SameECGTimeEGTPTDiffInterval.csv attached*
- 2) *Identical EGDTC, interval measurements but different EGTPT, see SameECGTimeIntervalDiffEGTPT.csv attached*
- 3) *Duplicate observations when ignoring EGSEQ*

Please correct the problems and resubmit a new EG.XPT file to your NDA. Please also send a courtesy copy to me via email.



%Sample# 0 0 0 0 Time# 0... %Sample# 0 0 0 0 Time# 0C...

Please confirm receipt and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
09/02/2014

PLANNING MEETING MINUTES

August 27, 2014

New NDA 206947

Lenvatinib

Eisai

Submission Date: August 14, 2014

Received Date: August 14, 2014

Proposed Indication: Progressive, radioiodine-refractory differentiated thyroid cancer

Core Review Team:

Patricia Keegan, Director DOP2 - ATTENDED

Deanne Varney, RPM - ATTENDED

Abhilasha Nair, Medical Officer - ATTENDED

Steven Lemery, Medical Officer Team Leader - ATTENDED

Janet Jiang, Statistics - ATTENDED

Kun He, Statistics Team Leader - ATTENDED

Jun Yang, Clinical Pharmacology

Hong Zhao, Clinical Pharmacology Team Leader - ATTENDED

Emily Fox, Non-Clinical - ATTENDED

Whitney Helms, Non-Clinical Team Leader - ATTENDED

Gaetan Ladouceur, CMC - ATTENDED

Amit Mitra, CMC - ATTENDED

Liang Zhou, CMC Team Leader - ATTENDED

Ali Al Hakim, CMC (Branch Chief)

Teicher Agosto, CMC (ONDQA RPM)

Anshu Marathe, Clinical Pharmacology/Pharmacometrics - ATTENDED

Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader – ATTENDED

Okpo Eradiri, Biopharmaceutics Reviewer

Angelica Dorantes, Biopharmaceutics Team Leader

Additional Attendees:

Paul Kluetz

Karen Jones

Carolyn Yancy

Stacy Shord

Frances Fahnbulleh

Ingrid Fan

Jeff Summers

Lauren Iacono-Connors

Otto Townsend

Hui-Lee Wong

Robert Wittorf

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Agenda Items:

1. Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
 - Will priority review be granted?

Discussion: This will likely be a standard review, but a final decision will be made by Friday, September 5, 2014.

- User Fee – Exempt due to orphan status
- Categorical Exclusion from environmental assessment requested
- Exempt from PREA due to orphan drug designation
- The clinical development of lenvatinib has been conducted under INDs (b)(4) and 113656

2. Milestone Dates: 8-Month Priority Review Clock

Discussion: These dates will change if priority review is not granted.

Milestone	8 month review
Acknowledgment Letter	August 28, 2014 <i>Issued XXX</i>
Priority Review Determination OR Filing Issues Identified/Not Identified Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting?	October 13, 2014
Filing Issues Identified (74 Day Letter) --- if not sent in Day 60 letter	October 27, 2014
Mid-Cycle Meeting	Month 3 – November 12, 2014
Mid-Cycle Communication	Month 3.5 – November 27, 2014
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 – January 16, 2015
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Month 5.25 (~mid-January)
Late Cycle Meeting Target Date	Month 6 if no AC (~mid-February)
Advisory Committee Target Date	Month 6 – February 12, 2015
Review Target Due Dates:	

<i>Primary Review Due</i>	Month 5 – January 14, 2015
<i>Secondary Review Due</i>	Month 5.1 – January 17, 2015
<i>CDTL Review Due</i>	Month 7 – March 19, 2015
<i>Division Director Review Due</i>	1.5 weeks pre-action – April 3, 2015
<i>Office Director Review Due/Sign-Off</i>	April 14, 2015
Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action – March 10, 2015
Compile and circulate Action Letter and Action Package	3 weeks pre-action – March 24, 2015
FINAL Action Letter Due	April 14, 2015

3. Potential Consults/Collaborative Reviewers Needed:

OPDP	<i>Consult sent 8/25/2014</i> Nick Senior (Reviewer) Jessica Cleck Derenick (TL) Olga Salis (RPM)
OSE	<i>Consult sent 8/25/2014</i> DPV: Tracy Salaam (TL), Afrouz Nayernama (Reviewer) DMEPA: Alice Tu (TL), Otto Townsend (Reviewer) DRISK: Doris Auth (TL), Carolyn Yancy (Reviewer) DEPI: Steven Bird (TL), Kate Gelperin (Acting TL), Hui-Lee Wong (Reviewer) Proprietary Name Review - request pending
Patient Labeling Team	<i>Consult sent 8/25/2014</i> Nathan Caulk (Reviewer) Barbara Fuller (TL)
SEALD	Ann Marie Trentacosti will attend labeling meetings and mentor ADL (Jennie Chang)
Maternal Health	<i>Consult sent 8/25/2014</i>
Facility/OMPQ	
OSI	Lauren Iacono-Connors assigned, need to select sites.
QT-IRT	<i>Consult sent 8/25/2014</i>
Pediatric Page/PeRC	Exempt due to orphan status Pediatric Page required before approval

	PeRC meeting not required
SGE's or Patient Representatives	Discussion: It was decided that both an SGE and patient representative will be required. The review team will determine who served as an SGE for the sorafenib efficacy supplement. OHCA will be contacted to determine a patient representative.

Are there any additional consults needed?

Discussion: No.

4. Upcoming/TBD Internal Team Meetings:

Discussion: It was noted that target dates will change if priority review is not granted.

- **Filing Meeting:** Scheduled for September 8, 2014.

**Please bring Filing review (TL signature) and Interim Deliverables
 - a. Please be prepared to identify significant filing issues for day 74 letter. The templates are available on the 21st Century website.
<http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm>
- **Mid-Cycle Meeting:** TBD, By November 12, 2014.
- **Mid-Cycle Communication Sponsor Tcon:** TBD
- **Labeling Meetings (suggested section groupings):** *When should we begin labeling meetings (Need to send proposed labeling to applicant on 1/16/2015)?*

Discussion: A determination regarding when labeling meetings should begin will be made after a decision has been made regarding priority review.

- a. _____ (Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions, Contraindications, Overdosage)
- b. _____ (Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations)
- c. _____ (CMC, Nonclinical, Clin Pharm Sections: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Clinical Pharmacology, Nonclinical Toxicology)

**Include OSE/CMC during this labeling meeting to review carton and container.

d. _____ (Highlights, Patient Counseling Information)

e. _____ (If needed)

- **Team Meetings and PMR/PMC Working Meetings:**

- Do we want to schedule monthly team meetings?

Discussion: The team would like monthly team meetings.

- Do we want to schedule separate PMC/PMR meetings?

Discussion: No, separate PMC/PMR meetings are not required. The team should notify the DDS of any proposed PMCs/PMRs that are not standard.

- **Wrap- Up Meeting:** TBD, By March 10, 2015.

5. **Applicant Orientation Presentation:** Scheduled for September 26, 2014.

6. **ODAC Needed/Not Needed:**

Discussion: The team determined that an advisory committee meeting is probably not needed because the application does not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease.

7. **Miscellaneous Items or Issues:**

- a. OSI inspections are needed, when does clinical/stats team need to pick the sites that will be inspected. Do we need any preclinical study site audits?

Discussion: Sites will be selected by 9/5/2014. OSI requested that DOP2 select a total of 6 sites to inspect. OSI will subsequently choose 4. OSI will also inspect the private company that conducted an independent review. An internal meeting will be scheduled with OSI and the clinical team to finalize site selection.

Preclinical study site audits will not be required.

- b. CMC/Teicher Agosto will assist with the following consults:
- Establishment (EES)/Coordinate Inspections

- Environmental Analysis: Request for Categorical Exclusion
 - Labeling
- c. **Discussion:** The review team determined that the compliance teams should be invited to the midcycle meeting, and should provide a slide identifying the sites to be inspected, when inspection will occur, and if an inspection waiver will be granted.

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/s/

DEANNE R VARNEY
08/28/2014

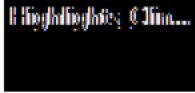
Varney, Deanne

From: Varney, Deanne
Sent: Thursday, August 28, 2014 2:39 PM
To: Susan_Mayer@eisai.com
Subject: NDA 206947 - Information Request

Hello Susan,

Please complete the attached Clinical Pharmacology and Cardiac Safety table and submit the completed table as an amendment to your NDA. Please also send me a courtesy copy via email.

Please confirm receipt and let me know should you have any questions.



Thank you,
Deanne

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

DEANNE R VARNEY
08/28/2014



NDA 206947

NDA ACKNOWLEDGMENT

Eisai, Inc.
Attention: Susan Mayer
Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

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

Name of Drug Product: Lenvatinib capsules, 4 mg and 10 mg

Date of Application: August 14, 2014

Date of Receipt: August 14, 2014

Our Reference Number: NDA 206947

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **October 13, 2014**, in accordance with 21 CFR 314.101(a).

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

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

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

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

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE on behalf of KAREN D JONES
08/28/2014



NDA 206947

MEETING REQUEST GRANTED

Eisai, Inc.
Attention: Susan Mayer
Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lenvatinib.

We also refer to your August 14, 2014, correspondence requesting an application orientation meeting.

The meeting is scheduled as follows:

Date: Friday, September 26, 2014
Time: 1:00PM – 2:00PM EST
Location: 10903 New Hampshire Avenue
White Oak Building 22, Room 2205
Silver Spring, Maryland 20903

FDA participants:

Patricia Keegan, Director DOP2
Deanne Varney, RPM
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistics
Kun He, Statistics Team Leader
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology Team Leader
Emily Fox, Non-Clinical
Whitney Helms, Non-Clinical Team Leader
Gaetan Ladouceur, CMC
Amit Mitra, CMC
Liang Zhou, CMC Team Leader
Ali Al Hakim, CMC (Branch Chief)
Jewell Martin and Teicher Agosto, CMC (ONDQA RPM)
Anshu Marathe, Clinical Pharmacology/Pharmacometrics
Liang Zhao, Clinical Pharmacology/Pharmacometrics Team Leader

Please e-mail me your attendee list at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Deanne Varney, 301-796-0297

If you have any questions, call me at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Deanne Varney
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Eisai
MEETING START DATE AND TIME	September 26, 2014, 1PM
MEETING ENDING DATE AND TIME	September 26, 2014, 2PM
PURPOSE OF MEETING	Application Orientation
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Deanne Varney, RPM, 22/2326, 6-0297
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

DEANNE R VARNEY
08/28/2014



IND 113656

MEETING MINUTES

Eisai, Inc.
Attention: Susan Mayer
Associate Director, Global Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lenvatinib (E7080)[ER-203492-13] [REDACTED] (b) (4) [REDACTED] Capsules).

We also refer to the meeting between representatives of your firm and the FDA on March 25, 2014. The purpose of the meeting was to present the high-level safety and efficacy data from Study E7080-G000-303 and to determine if the results of this single major efficacy trial would support submission of an NDA.

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

If you have any questions please call me at (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, March 25, 2014, 12:00PM
Meeting Location: White Oak Building 22, Room 1315

Application Number: IND 113656
Product Name: Lenvatinib
Indication: Radioiodine Refractory Differentiated Thyroid Cancer (DTC)
Sponsor/Applicant Name: Eisai, Inc.

FDA ATTENDEES (tentative)

Patricia Keegan, Director, DOP2
Jonathan Jarow, Deputy Director (Acting), OHOP
Ruthann Giusti, Clinical Reviewer, DOP2
Suzanne Demko, Clinical Team Leader, DOP2
Abhilasha Nair, Clinical Reviewer, DOP2
Steven Lemery, Clinical Team Leader, DOP2
Meredith Libeg, Regulatory Project Manager, DOP2
Stacy Shord, Clinical Pharmacology Reviewer, DCPV
Hong Zhao, Clinical Pharmacology Team Leader, DCPV
Nam Rahman, Supervising Pharmacologist, DCPV
Whitney Helms, Pharmacology/Toxicology Team Leader, DHOT
Liang Zhou, Chemistry Team Leader, ONDQA
Sirisha Mushti, Statistical Reviewer
Kun He, Statistical Team Leader
Otto Townsend, Reviewer, DMEPA
Meredith Libeg, Regulatory Project Manager, DOP2
Ingrid Fan, Regulatory Project Manager, DOP2
Ruth Maduro, Regulatory Project Manager, DOP2
Carolyn Yancey, Risk Management Analyst, OSE/DRISK

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor

SPONSOR ATTENDEES

Corina Dutcus, Senior Director, Clinical Research, Oncology
Matthew Guo, Senior Director, Biostatistics, Oncology
Alton Kremer, Deputy President, Oncology

Susan Mayer, Associate Director, Global Regulatory Affairs - Oncology
Robert Shumaker, Senior Director, Clinical Pharmacology/Translational Medicine, Oncology
Martina Struck, Acting President, Global Regulatory Affairs
Jon Sang Wong, Vice President, Global Regulatory Affairs - Oncology
Junming Zhu, Director Biostatistics, Oncology
Robert F. DeBenedetto, President and CEO, SFJ Pharmaceuticals, Inc.
Rolf Linke, CMO, SFJ Pharmaceuticals, Inc.

BACKGROUND

Clinical Development and Regulatory History:

Eisai describes lenvatinib as an oral, multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs including fibroblast growth factor receptor 1-4 (FGFR1-4), platelet-derived growth factor receptor α (PDGFR α), KIT, and receptor tyrosine kinase oncogene (RET).

Eisai has previously noted that the lenvatinib clinical development program consists of 18 dose-finding and activity-estimating trials in patients with various cancers [non-small cell lung cancer (NSCLC), melanoma, endometrial carcinoma, ovarian carcinoma, and advanced solid tumors], and eight pharmacokinetic (PK) or pharmacodynamic (PD) trials. Clinical pharmacology studies have evaluated lenvatinib PK and PD, including bioavailability of different formulations, food effects, drug-drug interactions (DDI), effects of hepatic and renal impairment and potential effects on the QT interval. Five activity-estimating trials evaluated the proposed dose regimen in patients with cancer, including two trials in patients with thyroid cancer (Studies 201 and 208). Two randomized, controlled efficacy trials [Protocol E7080-G000-303 and an additional trial evaluating efficacy in patients with hepatocellular cancer (HCC)] are ongoing; however, the final analysis of the primary endpoint for Protocol E7080-G000-303 has been conducted.

The IND [REDACTED] ^{(b) (4)} was submitted to FDA on March 31, 2005. An End-of-Phase 2 Meeting was held on January 12, 2011, to discuss the proposed design of E7080-G000-303 entitled, “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ¹³¹I-Refractory Differentiated Thyroid Cancer.” This trial was designed to demonstrate an improvement in median progression-free survival (PFS) with a hazard ratio of 0.57 (14 vs. 8 months) at a two-sided alpha of 0.01 (stratified log rank test). Eisai informed FDA that this single trial was intended to support registration. FDA agreed that PFS in a study that was well designed and conducted was acceptable as the primary endpoint for this trial provided that the trial demonstrated a robust, statistically persuasive, and clinically meaningful improvement in PFS with internal consistency of secondary endpoints and a favorable risk-benefit profile. FDA provided additional advice to Eisai concerning the statistical analysis plan for the trial and E7080-G000-303 was initiated under IND [REDACTED] ^{(b) (4)} on March 3, 2011.

A new IND (113656) was opened in DOP2 for the continued development of E7080 for the thyroid cancer indication. Orphan-Drug Designation was granted to lenvatinib on December 27, 2012 for “treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer.” A Type C meeting was held on September 18, 2013, to provide early guidance on the technical aspects of an NDA submission.

On January 24 2014, Eisai submitted a pre-NDA meeting request to present the high-level safety and efficacy data from E7080-G000-303, and to determine if the data are sufficient to permit submission of an NDA. The meeting package was submitted on February 25, 2014.

Eisai intends to submit an NDA for the following proposed indication:

“Lenvatinib is indicated for the treatment of adult patients with radioiodine-refractory differentiated thyroid cancer (DTC).”

NDA Submission in Support of the Proposed Indication

E7080-G000-30, also known as SELECT (“Study **E**7080 (**L**envatinib) in Differentiated **C**ancer of the **T**hyroid) is an ongoing, multicenter, double-blind, placebo-controlled trial which randomized 391 patients with histologically confirmed, measurable ¹³¹I-refractory DTC and radiographic evidence of disease progression within 12 months prior to enrollment to receive lenvatinib 24 mg daily (n=261) or matched placebo (n=131). Patients were enrolled at 150 sites in Europe, North America and the rest of the world (Chile, Japan, Korea, Russian Federation and Thailand). Randomization was stratified by geographic region (Europe, North America, Other), prior vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR)-targeted therapy (Yes or No), and age (≤ 65 years or > 65 years). Patients will continue study drug (lenvatinib or placebo) until documentation of disease progression, the development of unacceptable toxicity or withdrawal of consent.

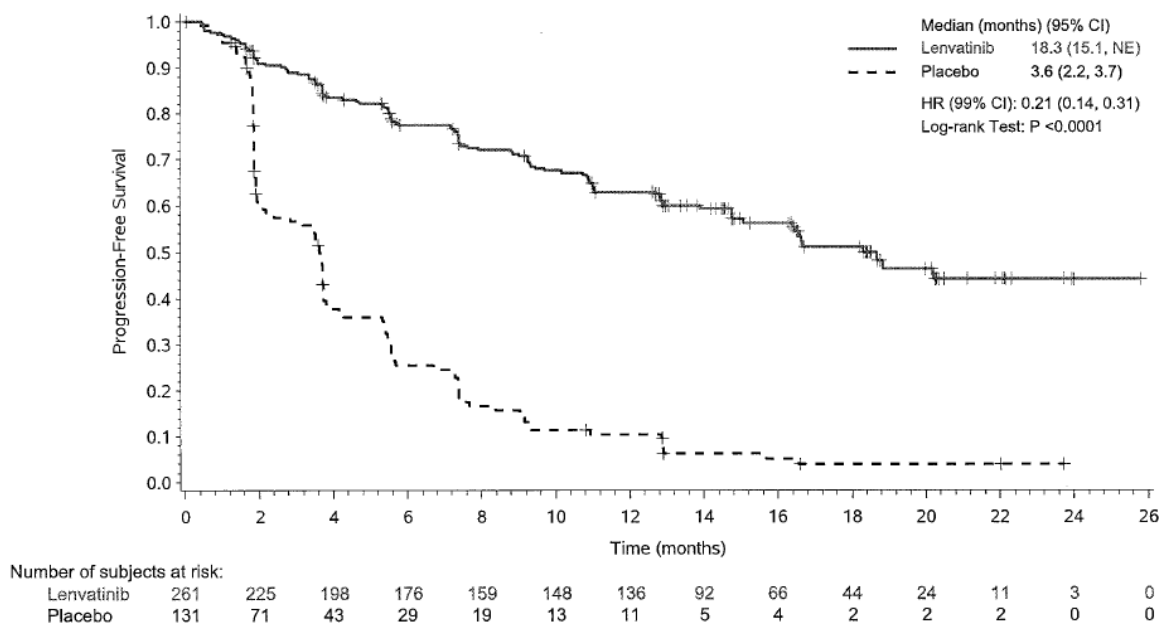
At the time of progression, patients randomized to placebo have the option to receive open-label E7080 until time of next disease progression. New baseline imaging studies will be obtained for these patients; however, independent confirmation of disease progression will not be obtained. Due to concerns raised by the Data Safety and Monitoring Committee (DMC) that excessive toxicity was experienced by patients receiving the 24 mg daily dose on the treatment arm of the E7080-G000-301 trial, the protocol was amended to lower the lenvatinib dose received in the open-label phase of the trial to 20 mg orally, once daily. All patients will be followed for survival.

The primary endpoint of the trial is progression free survival (PFS) as determined by the Independent Imaging Review Committee (IIR) blinded to treatment assignment, using RECIST criteria. Key secondary endpoints are objective response rate (ORR) and overall survival (OS). The sample size of 360 patients is based on the ability to detect a HR of 0.5714 for PFS with 90% power at a two-sided Type I error rate of 0.01, assuming a median PFS of 8 months in the placebo arm and median PFS of 14 months in the lenvatinib arm. The analysis of PFS was performed when 214 progression events (70% of subjects) occurred in the full analysis set as assessed by the IIR. The data cutoff for the primary study analysis occurred on

November 15, 2013. The primary test method is a stratified log-rank test. No interim analyses were planned for PFS. A stratified Cochran Mantel Haenszel (CMH) test for ORR and a stratified log-rank test for OS will be conducted if PFS reaches statistical significance, with hierarchical testing to adjust for multiplicity. The statistical analysis plan for the overall survival analysis did not specify the timing of the final or interim analyses of OS nor does it provide the power calculations or assumptions. The gate keeping procedure is proposed for adjusting overall alpha of 0.05 in the order of ORR and OS. All 392 patients were included in both the full analysis dataset used to evaluate effectiveness and in the safety dataset used in the safety analyses.

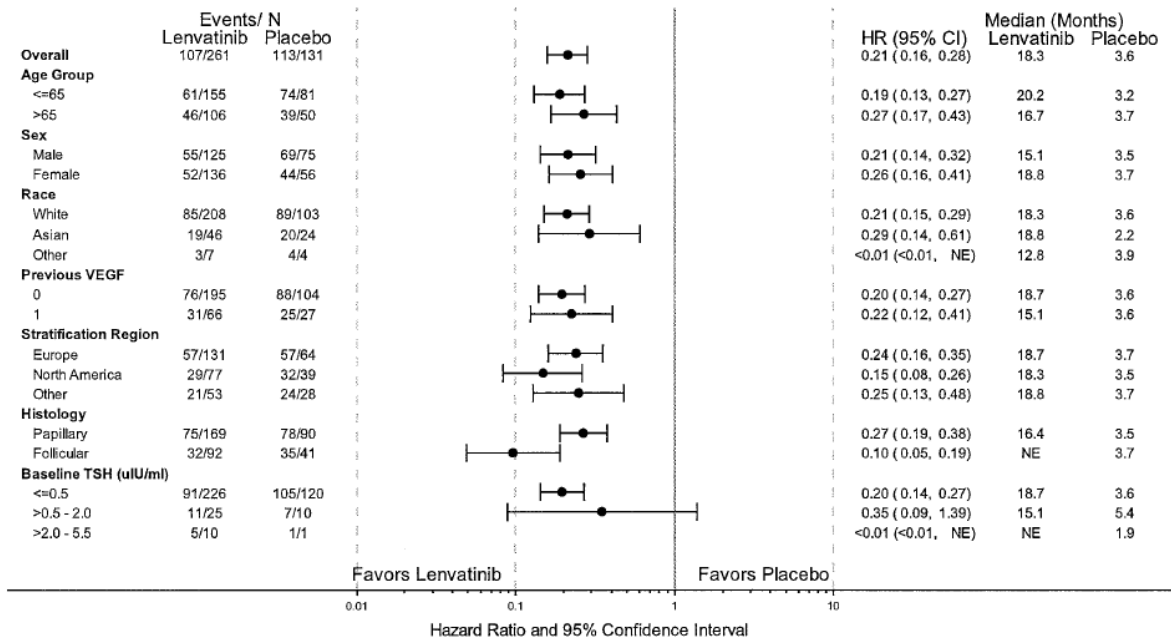
Eisai reports a median PFS of 18.3 months in the lenvatinib treated arm compared to 3.6 months in the placebo arm, with an HR of 0.21 (99% Confidence Interval [CI]: 0.14, 0.31) estimated from the stratified Cox proportional hazard model. This result was statistically significant: $p < 0.0001$ (stratified log rank test) (Figure 1).

Figure1. Kaplan-Meier Plot of Progression-Free Survival-Independent Review (Provided by Eisai as Figure 14.2.1)



Additionally, Eisai reports that PFS was prolonged with lenvatinib treatment in all subgroups including region, age group, prior VEGF/VEGFR therapy and histology (papillary, follicular (Figure 2). Results of the PFS analysis based on investigator assessment and based on the IRR review were reported to be similar.

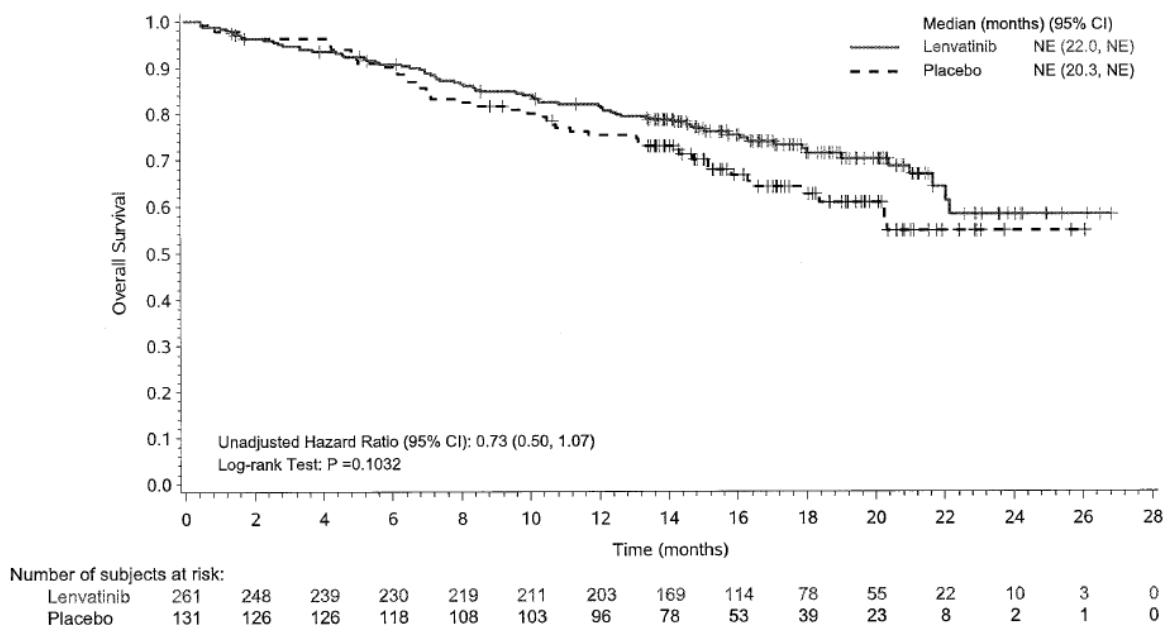
Figure 2. Forest Plot of Hazard Ratio for Lenvatinib vs Placebo in Progression-Free Survival – Independent Review
(Provided by Eisai as Figure 14.2.1.7.8)



Other Race group includes Black or African American, Native Hawaiian or other Pacific Islander, and Other
Median was estimated with Kaplan-Meier method and 95% confidence interval was constructed with a generalized Brookmeyer and Crowley method.
Hazard ratio is expressed as Lenvatinib/Placebo and was estimated from Stratified Cox proportional hazard model.
Program: R:\projects\le7080\g000-303\csr2014\comb\dev\pg\g_fas_forest_pfs.sas Data cutoff date 15NOV2013

The overall response rate (OR) based on IIR assessment was reported to be higher in the lenvatinib arm than in the placebo arm [65% vs 2%, $p < 0.0001$ (Cochran Mantel-Haenszel test)] and four patients on the lenvatinib arm were reported to have had a complete response. Median duration of response was unable to be estimated at the time of the data cutoff. A trend toward prolongation of overall survival (OS) at one year was reported; however, the median OS was unable to be estimated at the time of the data cutoff (Figure 3).

Figure 3. Kaplan-Meier Plot of Overall Survival- Unadjusted
(Provided by Eisai as Figure 14.2.2.1.1)



As of the data cutoff, treatment was ongoing for 122 (46.7%) patients receiving lenvatinib compared with 8 (6.1%) receiving placebo. A total of 109 patients receiving placebo had crossed over to open-label lenvatinib treatment at the time of the data cutoff. Almost all patients on the lenvatinib arm (99.6%) and in the placebo arm (90.1%) were reported to have had at least one treatment emergent adverse event (TEAE). Grade 3 TEAEs were reported in 85% of patients on the lenvatinib arm compared to 30% of patients on the placebo arm. Nonfatal serious adverse events (SAEs) were also reported more frequently in the lenvatinib arm (50%) compared to the placebo arm (23%). Fatal SAEs were reported in 8% of patients on the lenvatinib arm compared to 5% of patients on the placebo arm. Among patients treated with lenvatinib, 79% required at least one dose reduction, compared to 8% of patients treated with placebo. Among lenvatinib treated patients, 17% discontinued treatment due to a TEAE compared to 5% of placebo treated patients.

The most common TEAEs ($\geq 30\%$ in either arm, any grade) and occurring more frequently in the lenvatinib arm were reported to be: hypertension (69 vs 15); diarrhea (66% vs 17%); decreased appetite (53% vs 18%); weight decrease (51% vs 15%); nausea (46% vs 25%); fatigue (42% vs 24%); headache (38% vs 12%); stomatitis (36% vs 7%), vomiting 35% vs 15%), palmer-plantar erythrodysesthesia syndrome (PPES) (32% vs 1%); proteinuria (32% vs 3%), and dysphonia (31% vs 5%).

The most frequently reported ($\geq 5\%$) Grade 3 or 4 TEAEs were hypertension (43% vs 4%); weight decrease (12% vs 1%); proteinuria (10% vs 0); diarrhea 8% vs 0); asthenia (6% vs 2%); hypocalcemia (5% vs 0); decreased appetite (6% vs 1%); and fatigue (5% vs 2%). Deaths were reported in 27% of patients in the lenvatinib arm and 36% of patients in the placebo arm.

Most deaths in both arms were reported as due to disease progression and no pattern of fatal adverse events was reported.

Eisai states that the NDA will also include one supportive study:

E7080-G000- 201: Study 201 was an open-label, parallel cohort study that evaluated the anti-tumor activity, pharmacokinetics (PK), and safety of lenvatinib in patients with medullary thyroid cancer (MTC) and in patients with radioiodine-refractory DTC. The primary objectives of the study were to determine the objective response rate (ORR [CR + PR]) based on the modified Response Evaluation Criteria in Solid Tumors (RECIST) as assessed by the IIR, and to determine the PK profile and the PK/PD relationships of lenvatinib. A total of 117 patients (58 with DTC and 59 with MTC) were treated with lenvatinib. Two of the 117 patients were treated according to the regimen specified in the original protocol (10 mg BID), whereas the remaining 115 patients were treated according to the regimen specified by a protocol amendment (24 mg QD).

Eisai describes the efficacy results of Study 201 as follows:

In the DTC cohort,

- ORR was 50%, 59% in patients who had received prior VEGF-targeted therapy (n=17) and 46% in patients who had not received prior VEGFR-targeted therapy (n=41).
- The median duration of response was 12.7 months.

In the MTC cohort,

- ORR was 36% and was similar in patients with prior VEGF-targeted therapy (n=26) and those without prior VEGF-targeted therapy (n=33) (35% and 36%, respectively).
- The median duration of response could not be estimated with a minimum follow-up of 8 months.

E7080-J081- 208: Eisai has clarified that a second ongoing trial in this patient population (E7080-J081-208) was mandated by the Japanese Health Authority (PMDA) to further accumulate data for 131-I refractory DTC patients and to obtain data for medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC) patients in Japan only. Enrollment will continue in this trial until product approval in Japan. All patients in this study have received lenvatinib 24 mg QD for 28-day cycles. As of July 15, 2013, approximately 19 DTC patients, 8 ATC patients and 4 MTC patients had been enrolled. This trial is not intended to support efficacy in the US application.

Eisai has previously stated that the NDA will include approximately 1100 subjects from completed trials who have received lenvatinib monotherapy, including approximately 450 subjects with the target indication.

DISCUSSION

FDA notes that Eisai reported that 79% of the patients randomized to receive lenvatinib in E7080-G000-30 were unable to tolerate the starting dose of 24 mg daily and required dose reduction. FDA is concerned that the appropriate dose of lenvatinib has not been established for the treatment of patients with progressive 131I-refractory DTC. FDA requests that Eisai provide a discussion of ongoing or post-marketing studies that will be used to determine whether a lower dose or alternative dosing regimen may result in comparable efficacy with less toxicity in this patient population.

Eisai Emailed Response of 3/24/14: Eisai acknowledges the concern raised by FDA regarding the starting dose of the 24 mg regimen. Eisai will provide in the NDA a thorough dose justification including but not limited to the matters in item 17. Eisai agrees with FDA's request to discuss a post-marketing study that would determine whether a lower starting dose or alternative dosing regimen may result in comparable efficacy with less toxicity in this patient population. There is currently no ongoing study that will address that question.

Discussion During Meeting: FDA will consider optimal dosing based on data provided in the NDA and will consider the clinical outcomes data in the control arm that initiated treatment on crossover at 20 mg daily. FDA encouraged Eisai to provide a proposed protocol to further assess other dosing regimen as soon as possible with consideration that such a study could be concluded postmarketing, but initiated sooner. FDA agreed to work collaboratively with Eisai on development of such a proposed trial.

Clinical:

1. Does the FDA agree that efficacy and safety results from the Phase 3 registration study E7080-G000-303 are sufficient to permit submission of an NDA for lenvatinib in the treatment of adult patients with radioiodine-refractory DTC?

FDA Response: Yes, the summary data as presented by Eisai appear to be sufficient to support submission of an NDA. Note that the submission will be subject to a filing review to assess the adequacy of the submission.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

2. Does the FDA agree with the revised clinical data cutoff date (15 Sep 2013) for submission of safety information for the ongoing lenvatinib study?

FDA Response: FDA understands that Eisai is proposing moving the cutoff date from July 15, 2013 to September 15, 2013, due to the delay in achieving the 214th progression event in E7080-G000-303. Moreover, Eisai proposes that the cutoff date of September 15, 2013, be used to prepare a safety progress report for E7080J081-202 and E7080-J081-208. FDA notes that at the time of the data cutoff for the primary efficacy analysis, Eisai reported that treatment was ongoing for 122 patients (47%) randomized to

the lenvatinib arm; therefore, FDA requests clarification as to why additional follow-up data from these trials cannot be provided. A data cut-off for submission of safety data of no more than 6 months prior to the submission is more appropriate.

FDA requests further clarification concerning Eisai's proposal for submission of safety data from ongoing indications other than thyroid cancer (for example, E7080-J081-202, a Phase 2, non-randomized monotherapy trial of patients with hepatocellular carcinoma with hepatic impairment). FDA understands Eisai is proposing to provide clinical narratives for all SAEs and deaths occurring within 30 days of the last study treatment, including deaths due to disease progression, and that safety will be based upon preliminary data present in the unlocked clinical trial database which will not have been fully collected, reviewed, or clarified. FDA does not find this proposal to be acceptable. All safety data submitted to the NDA should be reviewed and verified. Clinical narratives should be identified in the Table of Contents under module 5.

Eisai's Emailed Response of 3/24/14: Eisai requests clarification of the Agency's comments relating to agreement with the proposed data cut-off date for submission of clinical safety information for the ongoing studies, revision to the cutoff date for the ISS and revision to the cut-off date for the safety update for completed studies where subject participation was ongoing (either on study drug or in follow up) at the time of the database lock used for preparation of the CSR. It is our understanding, as documented in the Memorandum of Meeting Minutes from the Type C Guidance Meeting which occurred on 18 September, 2013, the Agency had agreed to our original proposal of a clinical safety cut-off of 15 July 2013 for a targeted NDA submission of 30 March 2014. Due to the delay in achieving the 214th progression event in E7080-G000-303 the NDA submission date has shifted to end June/mid-July 2014. Reflective of this shift in submission date, Eisai has proposed to move the clinical safety cut-off day accordingly, to 15 September, 2013, capturing an additional 2 months of safety data to be submitted with the NDA.

Eisai wishes to clarify several points following Agency response:

- FDA stated in the Type C Advice Meeting Minutes (Question 6, Page 10) that, "In general, the cut-off data for the safety database should be within 6 months of the event driven cutoff for efficacy." In this NDA, the event driven cut-off date for Study E7080-G000-303 was 15 Nov 2013 and Eisai's proposed clinical cut-off date is 15 Sept 2013. The date is within FDA's recommendation.
- Eisai notes that almost all the ongoing patients in the lenvatinib development program are from Study E7080-G000-303 which is the major well controlled clinical study for this NDA. The data cut-off date for this study is 15 Nov 2013, and not 15 Sept 2013. Eisai expects the NDA to be submitted end June/mid July, making the difference between 6 months prior to NDA submission and the 15 Nov 2013 date about 6 to 8 weeks.

- Eisai proposed submission of progress reports for ongoing Studies (ie, E7080-J081-202, E7080-G000-205, E7080-G000-304, E7080-703, and E7050-G000-901) utilizing a cutoff date of 15 Sept 2013 for safety data. As documented in the Type C Advice Meeting Minutes (18 Sept 2013, Pg 8), the Agency agreed with the original proposal that the data-cut-off for safety would be July 15 2013 for all studies, except Study 303. Eisai plans to provide a full CSR for Study E7080-J081-208, utilizing the same cut-off date of 15 Sept 2013.
- For the ongoing non-randomized, monotherapy HCC Study E7080-J081-202 a tabular summary of all SAE's and deaths, as well as the clinical narratives will be provided
- For the ongoing combination Study E7050-G000-901 no summary of safety data will be provided.
- For ongoing randomized studies that are blinded to the Eisai medical personnel (ie, E7080-G000-205, E7080-G000-304, and E7080-703) no summary of safety data will be provided. SAE reports from patients enrolled in such studies will be provided if the blind on specific patients was broken.
- Eisai would like to clarify that the ongoing studies mentioned above (ie, E7080-J081-202, E7080-G000-205, E7080-G000-304, E7080-703, and E7050-G000 901) do not have locked databases and therefore data are not final. These are the only studies in the entire NDA submission for which completed CSRs can not be provided. For the studies identified above a progress report will be submitted (see Table below).
- Completed studies for which CSRs will be submitted in the NDA but have patients ongoing in an extension phase following the cut-off for the CSR include: E7080-E044-101, E7080-A001-102, E7080-G000-201, E7080-G000-203, E7080-G000-204, and E7080-G000-206. Eisai will submit a safety progress report covering the period between data cut-off for the CSR and 15 Sept 2013 for each of the identified studies. Eisai believes this was agreed to in the Type C Guidance Meeting (Pg 11).

Studies in Oncology Patients

Study No.	Phase	Patient Population	Treatment	Status/ Submission Format
E7080-E044-101	1	Solid tumors or lymphoma	Monotherapy	Completed w/ongoing patients (1 patient ongoing as of 15 Sept)/ Full CSR plus safety progress report ^a
E7080-A001-102	1	Solid tumors/ lymphomas or melanoma	Monotherapy/ Combination with TMZ	Completed w/ongoing patients (1 patient ongoing as of 15 Sept)/ Full CSR plus safety progress report ^a
E7080-J081-103	1	Solid tumors	Monotherapy	Completed/ Full CSR

Study No.	Phase	Patient Population	Treatment	Status/ Submission Format
E7080-E044-104	1	Solid tumors or lymphomas	Monotherapy	Completed/ Full CSR
E7080-J081-105	1	Solid tumors	Monotherapy	Completed/ Full CSR
E7080-J081-110	1	Advanced NSCLC	Combination with carboplatin + paclitaxel	Completed/ Full CSR
E7080-701	1b	Platinum-Sensitive Recurrent Ovarian Cancer	Combination with gem + carbo	Completed terminated early/ Full CSR
E7080-J081-202	1/2	Advanced HCC	Monotherapy	Ongoing/ Safety progress report ^a (tabular summary of SAE's/deaths, clinical narratives)
E7080-G000-205	1/2	Renal cell carcinoma.	Monotherapy/ Combination with everolimus	Ongoing/ Safety progress report ^a (no summary of safety data will be provided.. SAE reports from patients enrolled will be provided if the blind broken) Study blinded to the Eisai medical personnel
E7050-G000-901	1b/2	Solid Tumors (ph 1b) Glioblastoma or Melanoma (ph 2)	Combination with E7050 (golvatinib)	Ongoing/ Safety progress report ^a (no summary of safety data will be provided)
E7080-702	1b/2	Melanoma	Combination with DTIC	Completed/ Full CSR
E7080-G000-203	2	Recurrent malignant glioma	Cohort 1: Monotherapy, Bevacizumab controlled Cohort 2 /3: Monotherapy	Completed w/ongoing patients (0 patients ongoing on lenvatinib as of 15 Sept)/ Full CSR plus safety progress report ^a
E7080-G000-204	2	Endometrial cancer	Monotherapy	Completed w/ongoing patients (7 patients ongoing as of 15 Sept)/ Full CSR plus safety progress report ^a
E7080-G000-206	2	Melanoma	Monotherapy	Completed w/ongoing patients (4 patients ongoing as of 15 Sept)/ Full CSR plus safety progress report ^a

Study No.	Phase	Patient Population	Treatment	Status/ Submission Format
E7080-703	2	Nonsquamous NSCLC.	Monotherapy Placebo-controlled	Ongoing/ Safety progress report ^a (no summary of safety data will be provided). SAE reports from patients enrolled will be provided if the blind broken) Study blinded to the Eisai medical personnel
E7080-J081-208	2	Thyroid Cancer (DTC, MTC and ATC)	Monotherapy	Ongoing (25 patients ongoing 15 Sept)/ Full CSR ^a
E7080-G000-201	2	Thyroid cancers (DTC and MTC)	Monotherapy	Completed w/ongoing patients (9 patients ongoing as of 15 Sept)/ Full CSR plus safety progress report ^a
E7080-G000-303	3	Iodine Refractory (DTC)	Monotherapy Placebo controlled	Completed/ Full CSR ^b (ongoing as of 15 Nov 122 patients in randomized lenvatinib arm, 8 patients in randomized placebo group, 58 patients in OOL)
E7080-G000-304	3	HCC	Monotherapy Sorafenib controlled	Ongoing/ Safety progress report ^a (no summary of safety data will be provided). SAE reports from patients enrolled will be provided if the blind broken). Study blinded to the Eisai medical personnel

^a clinical cut-off date of 15 Sept 2013

^b event driven cut-off date of 15 Nov 2013

Discussion During Meeting: FDA clarified that a complete safety database (through the data cut-off date) is expected at the time of the initial NDA submission and that additional safety data in the 120-day safety update should be minimal. The cut-off date for the data from the studies which will support safety should be no more than six months prior to the date of the NDA submission. Eisai agreed to reset the safety data cut-off period for Study E7080-G000-303 to February or March 2014, for incorporation in the ISS data sets. All other study cut-off periods will remain September 15, 2013. Eisai agreed to provide a safety update, in text, summarizing the additional safety information occurring since the safety data cut-off used in the CSR for Study E7080-G000-303. The 120 day safety update cut-off will be approximately June 2014,

and the submission will include narrative summaries for any patient deaths on treatment, any new SAEs, and any patient who discontinued treatment due to adverse events.

3. Does the FDA agree that the revision to the cutoff date for the ISS to September 15, 2013, is appropriate?

FDA Response: Please see FDA's response to Eisai's question #2 above.

Eisai's Emailed Response of 3/24/14: See Eisai Emailed Response to Question 2 above.

Discussion During Meeting: Please refer to "Discussion During Meeting" under Question 2.

4. Does the FDA agree with the revision to the cutoff date to September 15, 2013, for the safety update for completed studies where subject participation was ongoing (either on study drug or in follow up) at the time of the database lock used for preparation of the CSR?

FDA Response: FDA does not agree. Please see FDA's response to Eisai's question #2 above.

Eisai's Emailed Response of 3/24/14: See Eisai Emailed Response to Question 2 above.

Discussion During Meeting: Please refer to "Discussion During Meeting" under Question 2.

5. Does the FDA agree with Eisai's revised proposal regarding images from Study E7080-J081-208?

FDA Response: Yes, FDA agrees with Eisai's proposal not to make radiographic images from this study available for review since E7080-J081-208, with a very small number of patients with 131-I refractory DTC, is not intended to support efficacy. Because E7080-G000-201 will be used to support the regulatory filing, Eisai will need to be prepared to make radiographic images from this study available for review upon request.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

6. Does the FDA agree with the revised proposal for the cutoff date for the 120-day safety update?

FDA Response: No. FDA does not find the proposed cutoff date for the 120-day safety update of May 15, 2014 to be acceptable relative to the proposed data base cutoff of September 15, 2013.

Eisai's Emailed Response of 3/24/14: Eisai requests clarification of the Agency's comments relating to agreement with the proposed cut-off date for the 120-day safety update. It is our understanding, as documented in the Memorandum of Meeting Minutes (Pg 11) from the Type C Guidance Meeting that all safety updates were to be provided in the NDA through 15 July 2013 and that Eisai supplement with additional events through the data cut-off date at the time of the 120-day safety update. Further, agreement was reached that the cut-off date for the 120-day safety update should be 4 to 6 months following the cut-off date of the safety data for the original NDA. Our revised proposal of a data cut off of 15 May 2014 for the 120-day safety update is 8 months following the proposed cut-off date (15 Sept 2013) of the safety data for the original NDA and therefore provides more safety data than originally agreed.

Discussion During Meeting: Please refer to "Discussion During Meeting" under Question 2.

7. Does the FDA agree to the inclusion of an evaluation of the efficacy and safety of lenvatinib in the context of the historical data for sorafenib in the Clinical Overview?

FDA Response: FDA agrees that inclusion of an historical overview of the efficacy and toxicity of approved agents is relevant to provide a context for the submission and recommends that this information be incorporated into the integrated summary of effectiveness (ISE) and the integrated summary of safety (ISS) in module 2.5. However, FDA cautions Eisai against cross-study comparisons both in the final study report and in labeling. Module 2.5

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Clinical Pharmacology:

8. Does the FDA agree to the slight modification (addition of study E7080-A001-008) to the studies which will be pooled to assist in pharmacokinetic (PK) model development and to better characterize covariates influencing lenvatinib PK?

FDA Response: Yes.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

9. Does the FDA agree to the revised data cutoff date (15 Sep 2013) for the PK and PK/Safety data for the ongoing studies apart from study E7080-J081-208 which will remain as originally agreed (15 Jul 2013)?

FDA Response: Yes.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

NDA Table of Contents:

10. Does the FDA agree with the proposed content for the complete application?

FDA Response: No. FDA has the following comments concerning the proposed content for the NDA submission:

- a. Concerning section 5.3.5.4, Reports of efficacy and safety studies [Thyroid Cancer], Other Study Reports, provide reports only from monotherapy trials. For these trials, provide only a protocol synopsis, a table of current enrollment, and a tabular summary of serious adverse events (SAEs) and deaths occurring within 30 days of the last study treatment.
- b. Do not include reports from randomized trials in which the study blind has not been broken. However, provide SAE reports from patients enrolled in such studies if the blind on specific patients was broken (e.g., as necessary for the care of the patient).
- c. Concerning section 5.3.7, Case-report Forms and Datasets, submit only reviewed, verified and locked datasets.

In addition, please see clinical comment #12 and statistics comment #14 and 16 below.

Eisai's Emailed Response of 3/24/14: Eisai requests clarification regarding the Agency's comments on the proposed content for the NDA table of contents. In particular, point a) concerning section 5.3.5.4, Other Study Reports. Eisai understand this section should include:

- Reports of interim analyses of studies pertinent to the claimed indication (There are no such reports for this NDA submission).
- Reports of controlled safety studies not reported elsewhere (There are no such reports for this NDA submission).
- Reports of controlled or uncontrolled studies not related to the claimed indication. These include studies E7080-J081-110, E7080-G000-203, E7080-G000-204, E7080-G000-206, E7080-701and E7080-702.
- Reports of ongoing studies. These include Studies E7080-J081-202, E7080-G000-205, E7080-G000-304, E7080-703, and the combination study E7050-G000-901.

Discussion During Meeting: FDA stated that single arm studies of lenvatinib in combination with other drugs or where lenvatinib is administered in blinded studies where the blind has not been broken, will provide little insight into the safety or efficacy of lenvatinib, and the FDA will not perform an exhaustive review of these studies. However, FDA agreed to Eisai's proposal to include reports from these studies in the NDA for completeness.

ADDITIONAL COMMENTS:

Clinical:

11. In the original NDA submission, please provide a separate analysis of safety among patients in the open-label extension phase of the E7080-G00-303 study. This should include cumulative data concerning exposure, subject disposition with reasons for treatment discontinuation, TEAEs (serious and fatal), a table showing the per-patient incidence of toxicities by MedDRA primary term and system/organ/class (SOC) category for CTCAE Grades 1-5 and Grades 3 and 4. Provide clinical narratives for all SAEs and deaths occurring within 30 days of the last study treatment including deaths attributed to disease progression with an ongoing SAE at the time of death.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

12. In the label, if appropriate and applicable, describe safety using laboratory variables rather than investigator-reported assessments.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Statistics:

13. Include the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

Eisai's Emailed Response of 3/24/14: Please confirm this request is limited to the Phase 3 pivotal Study E7080-G000-303.

Discussion During Meeting: FDA stated that if Eisai plans to use any additional studies to support labeling or promotional materials, the datasets and SAS programs for those studies should be included in the original NDA submission. Eisai acknowledged FDA's recommendation and will take it under advisement.

14. Provide SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert.

Eisai's Emailed Response of 3/24/14: Please confirm this request is limited to the Phase 3 pivotal Study E7080-G000-303.

Discussion During Meeting: Please refer to "Discussion During Meeting" under Question 13.

15. Provide a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined PFS (or investigator assessed PFS) event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity Analysis of the SAP should be included as well.

- Provide raw and derived datasets with adequate documents(s) in PDF file (define.pdf). In the define document, please provide adequate comment for variable label, data format decode of categorical and numerical variable(s), and algorithm(s) to derive new variable from raw data to derived data.
- Provide executable SAS program(s) with adequate document(s) to duplicate the analysis datasets derivation from raw datasets.
- Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
- Provide SAS programs with adequate document(s) for the derived datasets and the analyses associated with the results presented in the proposed package insert.

Eisai's Emailed Response of 3/24/14: Eisai request confirmation of the following:

- The request is limited to the Phase 3 pivotal Study E7080-G000-303.
- In the first bullet point, the Agency's reference to providing raw dataset refers to the SDTM datasets.
- All programs should follow e-submission standards as .TXT file.
- Does the Division agree that since there is no location within the eCTD structure to accommodate the mock-up define file request, this information should be submitted separately at the time of NDA submission?

Discussion During Meeting: In response to Eisai's request, under bullet one of the emailed responses of March 24, 2014, to confirm that it is acceptable limit submissions of datasets and SAS Programs to the Phase 3 pivotal Study E7080-G000-303, please refer to "Discussion During Meeting" under Question 13.

In regards to the second bullet of the emailed responses of March 24, 2014, FDA clarified that it refers to SDTM datasets.

In response to Eisai's request for clarification, under bullet three of the emailed responses of March 24, 2014, FDA confirmed that all programs should follow e-submission standards as .TXT file.

In regards to the fourth bullet of the emailed responses of March 24, 2014, FDA clarified that the mock-up define files should be placed in the same eCTD structure location as the program files.

Clinical Pharmacology:

In addition to addressing the comments conveyed in the September 18, 2013 meeting minutes, including the following in the NDA submission,

16. Provide a table that compares the pharmacokinetics of lenvatinib across the different patient populations in the Summary of Clinical Pharmacology, as different dose and schedules are recommended for different patient populations.

Eisai's Emailed Response of 3/24/14: Eisai wishes to clarify that with the exception of the HCC indication, the 24 mg starting dose regimen has been used for all Phase 2 and Phase 3 studies. Therefore, Eisai requests confirmation that when the Agency requests a table comparing the pharmacokinetics of lenvatinib in the Summary of Clinical Pharmacology, they refer to a comparison based on demographic information.

Discussion During Meeting: FDA clarified that the NDA submission should include a comparison of the pharmacokinetic parameters in the different cancer populations and that Eisai should include the underlying cancer disease as a covariate in the population pharmacokinetics analysis. Eisai acknowledged and agreed with FDA's recommendation.

17. Provide a comprehensive rationale for clinical dose selection, duration of exposure, reasons for dose reduction, interruption or discontinuation, the maximum tolerated dose, nonclinical pharmacology and PK/PD studies, and relevant biomarkers in thyroid cancer in the Summary of Clinical Pharmacology.

Eisai's Emailed Response of 3/24/14: Eisai wishes to confirm that a comprehensive rationale for clinical dose selection will be included in the NDA submission. Based on the Memorandum of Meeting Minutes from the Type C Guidance Meeting (Pg. 17), Eisai understands our agreement to supply biomarker data other than specific DMET data (ie, cytokine and angiogenic factor, CAF) to be submitted as SAS transport files along with providing the data via line listing in the individual CSRs.

Discussion During Meeting: FDA agreed with Eisai's proposal to provide a rationale for clinical dose selection in the original NDA submission and Eisai confirmed that they will provide SAS transport files and data supporting the dose selection.

18. Provide a rationale for excluding one patient from the proposed population pharmacokinetic and exposure-response analyses.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

19. Include measurements of baseline thyroid function as a covariate in the population pharmacokinetic analysis.

Discussion During Meeting: Eisai acknowledged and agreed with FDA's response. There was no discussion during the meeting.

Division of Medication Error Prevention and Analysis (DMEPA)

20. DMEPA does not have any comments in regards to the questions contained within the briefing package; however, it is recommended that Eisai submit a proprietary name for review if Eisai intends to have one for this product. (See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>).

Eisai's Emailed Response of 3/24/14: On 10 January 2013, Eisai submitted a request for review of proposed proprietary name, Lenvima to DMEPA. On 07 July 2013 Eisai received notification that the name was conditionally approved. As requested in the 07 July correspondence, Eisai will submit a request to the NDA, as the packaging configuration has changed since the original submission in January 2013.

Discussion During Meeting: FDA acknowledged Eisai's emailed response. There was no discussion during the meeting.

Discussion of the Content of a Complete Application

- The content of a complete application was discussed. Eisai proposes to submit a complete application with no late components. As a result, major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Since Eisai stated their intent to submit a complete application and therefore, there were no agreements for late submission of application components.
- Eisai agreed to include a comprehensive and readily located list of all clinical sites and manufacturing facilities to be included or referenced in the application.
- A preliminary discussion on the need for a REMS was held and it was concluded that based on a preliminary evaluation, a REMS will not be required for filing of the NDA.

However, a formal determination on the need for a REMS will be a review issue for the NDA.

PREA Requirements

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Prescribing Information

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

Manufacturing Facilities

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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/s/

MEREDITH LIBEG
04/15/2014



FOOD AND DRUG ADMINISTRATION

Meeting Date and Time: January 12, 2011, 1:00 p.m.

Meeting Type: Type B meeting

Meeting Category: End of Phase II (Teleconference)

Meeting Location: CDER WO 3201

Application Number: IND (b) (4)

Product Name: E7080

Received Briefing Package November 23, 2010

Sponsor Name: Eisai Inc.

Meeting Requestor: Ana Arango Bossard, MT. (ASCP), MBA

Meeting Chair: Virginia Kwitkowski, MS, RN, ACNP-BC,
Acting Clinical Team Leader, DDOP

Meeting Recorder: CDR Diane Hanner, M.P.H., M.S.W.

Meeting Attendees:

- Mark Taisey, Vice President, Regulatory Affairs
- Ana Arango Bossard, MT(ASCP), MBA, Associate Director, Regulatory Affairs, Oncology
- Alton Kremer, M.D., Ph.D., Senior Vice President, Clinical Oncology
- James P. O'Brien, M.D., Executive Director, Clinical Oncology
- Kun Chen, Ph.D., Director, Biostatistics

FDA Attendees:

- Robert Justice, M.D., Division Director, DDOP
- Virginia Kwitkowski, MS, RN, ACNP-BC, Acting Clinical Team Leader, DDOP
- Hong (Laura) Lu, Biostatistics Reviewer, DBV
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DDOP

IND (b) (4)

BACKGROUND

Eisai submitted a Type B meeting request on October 21, 2010, to discuss the planned Phase 3 pivotal trial to support registration for E7080 in radioiodine (^{131}I) refractory differentiated thyroid cancer. Responses in patients with ^{131}I refractory differentiated thyroid cancer have been observed in the Phase 2 program.

Clinical Development Questions

Question 1: Eisai plans to conduct a single pivotal randomized double blind, placebo-controlled Phase 3 clinical trial (E7080-G000-303) to support registration of E7080 for treatment of patients with ^{131}I -Refractory Differentiated Thyroid Cancer. This study will utilize the primary endpoint of progression-free survival.

a. Does the Division agree with the approach of having progression-free survival as the primary endpoint as described?

FDA Response: Yes, PFS is acceptable as the primary endpoint in this trial of patients with ^{131}I -Refractory Differentiated Thyroid Cancer. However, the acceptability of PFS results will be dependent upon a robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile. You should also be aware that PFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates between treatment arms or missing data. We also discourage using interim results of PFS to make a claim of efficacy. We do not recommend the conduct of an interim analysis of PFS. Evidence should be provided that statistical significant results on PFS correspond to clinical benefit.

b. Does the Division agree that a single pivotal trial supported by Phase 2 data could be considered adequate to support a marketing application?

FDA Response: For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically and clinically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.

Question 2: Eisai proposes that a demonstration of an approximately 75% improvement in median Progression-Free Survival (H.R. = 0.57), that is statistically significant at a 2 sided alpha = 0.01 (stratified log rank test), would provide evidence of clinical benefit sufficient to support a marketing application for this indication.

Does the Division agree with the proposed primary analysis and magnitude of clinical effect (H.R. = 0.57 for PFS) to support a marketing application in this patient population?

FDA Response: Yes, the proposed analysis is acceptable, however whether the magnitude of effect is adequate to support marketing approval is a review issue based upon the risk: benefit assessment conducted during the Agency review of the trial data.

IND (b) (4)

Question 3: For the planned Phase 3 trial (E7080-G000-303), Eisai has designed the study to ensure that a rigorous and robust assessment of PFS, as outlined in the supporting text, can be performed.

Does the Division agree that Eisai has employed all appropriate available measures to ensure the integrity of PFS determinations?

FDA Response: Yes, it appears that most sources of possible bias have been minimized in the proposed trial design. However, the integrity of the PFS determinations may still be impacted by missing data or premature assessments that may be conducted due to inadvertent unblinding due to adverse reactions.

Question 4: At the time of disease progression, without breaking the blind, patients randomized to either placebo or E7080 will have the option, at the discretion of the investigator, to receive open-label E7080 until time of next disease progression.

Does the Division agree with the proposed open-label extension?

FDA Response: Open-label extension, which may confound the OS analysis, will be at the risk of the Sponsor. No agents have demonstrated OS benefit in this disease setting, so we disagree with your statement that OS confounding will occur even without crossover.

We do not agree that patients with disease progression on E7080 should be continued on the drug. If you believe there may be benefit to continuing the drug in these patients you should re-randomize patients to continuing the drug or not.

Question 5a. Does the Division agree with the trial design, specifically the statistical analysis, as contained in the protocol?

FDA Response: No. See responses above.

Meeting Discussion: The sponsor clarified that they would not conduct an interim analysis of PFS for efficacy and that only patients who received placebo prior to progression of disease would be eligible to receive E7080 upon progression.

Question 5b. Does the Division agree with the trial design, specifically the proposed stratification of the randomization?

FDA Response: No, we recommend that you also stratify by age (≤ 65 years vs. > 65 years).

Meeting Discussion: The sponsor proposes to remove histology as a stratification factor, and to add "prior VEGF therapy" and "age" as stratification factors. The division recommended against removal of histology as a stratification factor and that any imbalance in histology between arms could confound interpretation of the trial results and would be their risk. It would be important to collect and submit histology data with the clinical study report.

The stratified analysis is the primary analysis for this trial. If the sponsor finds that they would prefer an un-stratified analysis they should propose a justification to the agency.

IND (b) (4)

Question 5c. Does the Division agree with the trial design, specifically the study population, as defined by the key inclusion/exclusion criteria noted below?

FDA Response: No. See responses above. The inclusion/exclusion criteria appear acceptable.

Question 6: The proposed design for the clinical trial employs the use of a placebo control.

Does the Division agree with the use of placebo as the control?

FDA Response: Yes.

Question 7: Eisai anticipates that the proposed safety database will consist of approximately 670-854 subjects treated with 24 mg once daily E7080 of which 294 are ¹³¹I-refractory differentiated thyroid cancer subjects (~238 subjects treated in study E7080-G000-303 and 56 subjects treated in study E7080-G000-201).

Does the Division agree that this safety database would be sufficient to support the marketing application of E7080?

FDA Response: Yes.

Question 8: Eisai plans to request orphan drug designation for E7080 for the treatment of ¹³¹I-Refractory Differentiated Thyroid Cancer. In accordance with 21 CFR 314.55 (d), if a product has been granted orphan drug designation for an indication, submission of pediatric data is not required and a waiver is not needed. If orphan drug designation is granted, Eisai will not present a pediatric assessment for this indication.

Does the Division agree with this plan?

FDA Response: Yes.

IND (b) (4)

Additional Comments:

1. A clinical drug interaction study with a potent CYP3A4 inducer (such as rifampin) to assess its effect on the PK of E7080 is recommended.

2. In terms of inhibition potential of E7080 on major CYP enzymes, an estimated [I]/K_i ratio greater than 0.1 is considered positive and a follow-up *in vivo* evaluation of the E7080 inhibition potential with a sensitive substrate is recommended.

Please refer to

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf> for more information.

3. Depending on the results from your ongoing mass balance study (E7080-E044-104), a clinical study to evaluate the impact of renal impairment on the PK of E7080 may be warranted.

4. Please submit the study protocols for your planned Study E7080-A001-004 and Study E7080-A001-006 for FDA review prior to commencing the studies.

Meeting Discussion: The Sponsor stated that they had submitted the study protocol for E7080-A001-004 to the IND on January 7, 2011.

5. Missing data/assessments of progression should be kept at a minimum. A substantial amount of missing data or events could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS. Sensitivity analyses, including the worst comparison case treating lost-to-follow-ups (missing at least one tumor assessment before data cutoff) as events in the experimental arm and as censored in the control arm, should be performed to assess the robustness of the result of the primary analysis of PFS.

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/s/

VIRGINIA E KWITKOWSKI
01/12/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206947

LATE-CYCLE MEETING MINUTES

Eisai, Inc.
Attention: Susan Mayer
Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lenvatinib.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 4, 2015.

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

If you have any questions, call Deanne Varney, Regulatory Project Manager at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D.
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: Wednesday, February 4, 2015, 10:00AM – 11:00AM
Meeting Location: WO Building 22, Room 1309

Application Number: NDA 206947
Product Name: Lenvatinib
Indication: Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.
Applicant Name: Eisai, Inc.

Meeting Chair: Steven Lemery
Meeting Recorder: Deanne Varney

FDA ATTENDEES

Patricia Keegan, Director DOP2
Deanne Varney, Regulatory Project Manager
Monica Hughes, Chief, Project Management Staff
Abhilasha Nair, Medical Officer
Steven Lemery, Medical Officer Team Leader
Janet Jiang, Statistical Reviewer
Kun He, Statistical Team Leader
Jun Yang, Clinical Pharmacology Reviewer
Emily Fox, Non-Clinical Reviewer
Stephanie Aungst, Non-Clinical Reviewer
Whitney Helms, Non-Clinical Team Leader
Ali Al Hakim, ONDQA (Branch Chief)
Robert Wittorf, OMPQ
Carolyn Yancey, DRISK
Miriam Dinatale, DPMH

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese

APPLICANT ATTENDEES

Nancy Bower, Senior Director, Global Regulatory Affairs - Nonclinical
Corina Dutcus, Executive Director, Clinical Research, Oncology
Matthew Guo, Executive Director, Biostatistics, Oncology
Huguette Bodo-Kamga, Global Regulatory Affairs, Manager Labeling
Alton Kremer, Deputy President, Oncology
Simon Lin, Director, Statistical Programming – Oncology

Susan Mayer, Director, Global Regulatory Affairs – Oncology
Robert Shumaker, Senior Director, Clinical Pharmacology and Translational Medicine, Oncology
Martina Struck, President, Global Regulatory Affairs
Dimitris Voliotis, VP Clinical Research, Oncology
Sang Wong, Vice President, Global Regulatory Affairs - Oncology
Junming Zhu, Director Biostatistics, Oncology
Rolf Linke, MD, CMO SFJ Pharmaceuticals, Inc.

BACKGROUND

NDA 206947 was submitted on August, 14, 2014, for lenvatinib.

Proposed indication: Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

PDUFA goal date: April 14, 2015

FDA issued a Background Package in preparation for this meeting on January 22, 2015.

DISCUSSION

1. Introductory Comments and General Issues

Discussion:

FDA provided an overview of the FDA Trials Snapshot website and explained that FDA is providing Eisai the opportunity to populate the data tables in order to ensure that the data provided on the website is an accurate reflection of the data. FDA stated that Eisai is not required to provide the data and that the Professional Affairs and Stakeholders Engagement (PASE) team will use information from FDA reviews if the data are not provided. FDA noted that the PASE team will use the data tables provided to draft the Snapshot and the Division will review the Snapshot prior to publication on the website. Eisai confirmed that they will provide the populated data tables by Wednesday, February 11, 2015.

FDA noted that a draft of the ASCO Burst will be sent to Eisai for review prior to taking action on the application. FDA also stated that the Agency ultimately plans write a journal article regarding the FDA review of lenvatinib and will plan to send a copy of the paper to Eisai for comment prior to publication. Eisai confirmed that the study results will be published on February 12, 2015.

Eisai confirmed that they were previously informed that there were no findings at the Patheon-Burlington manufacturing site inspection.

Eisai noted that a Phase 2 renal cell carcinoma study (lenvatinib combined with everolimus) returned positive results. (b) (4)

(b) (4)

Eisai noted that the hepatocellular carcinoma study will complete enrollment summer 2015.

2. Review of Postmarketing Requirements and Commitments

- a. **Clinical Post-Marketing Requirement:** Conduct a clinical trial to evaluate whether an oral starting dose of 20 mg or 14 mg daily will have a better safety profile than the 24 mg starting dose, with a comparable objective response rate. Safety assessments will include evaluations for \geq Grade 3 adverse reactions, all adverse reactions, and serious adverse reactions.

PMR Milestone Dates:

Submit Draft Protocol (3 months before final protocol submission): 04/15 (*based on projected action date*)

Final Protocol Submission: 07/15

Trial Completion: 07/19

Final Clinical Trial Report Submission: 07/20

- b. **CMC Post-Marketing Commitment:** Submit a prior approval supplement (PAS) with a request to sunset the test and acceptance criterion based on the submitted data with the following information:

- A limit test for level (b) (4) of the drug substance in the drug product including the analytical method and its validation.
- Supporting data for the limits.

PMC Milestone Date:

PAS Submission: 06/15

Discussion: Eisai confirmed that the PMR draft protocol will be submitted in April 2015 regardless of the action date.

3. Labeling Issues

Discussion: Eisai and FDA reviewed labeling (PI and PPI) sent to Eisai on February 3, 2015. There were no major issues to discuss, and all minor issues were agreed on. Eisai asked FDA to consider a rounding issue in Table 4 of the PI. FDA will consider the request and will return updated labeling to Eisai by February 5, 2015.

4. Review Plans

Discussion: FDA confirmed that a mid-February action is being targeted.

5. **Wrap-up and Action Items**

Discussion: FDA reiterated the target action date of mid-February and stated that updating labeling will be provided to Eisai on February 5, 2015.

Please note that this application has not yet been fully reviewed by the signatory authority and division director and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

STEVEN J LEMERY
02/09/2015



NDA 206947

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Eisai, Inc.
Attention: Susan Mayer
Director, Regulatory Affairs
155 Tice Blvd.
Woodcliff Lake, NJ 07677

Dear Ms. Mayer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lenvatinib.

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 4, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Deanne Varney, Senior Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: Wednesday, February 4, 2015, 10:00AM – 11:00AM
Meeting Location: WO Building 22, Room 1309

Application Number: NDA 206947
Product Name: Lenvatinib
Indication: Treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.
Applicant Name: Eisai, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority and the division director and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

Discipline Review Letters

No Discipline Review letters will be issued.

Substantive Review Issues

There are no substantive review issues at this time.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. **Introductory Comments** – 5 minutes: Welcome, Introductions, Ground rules, Objectives
2. **Review of Postmarketing Requirements and Commitments** – 5 minutes
 - a. **Clinical Post-Marketing Requirement:** Conduct a clinical trial to evaluate whether an oral starting dose of 20 mg or 14 mg daily will have a better safety profile than the 24 mg starting dose, with a comparable objective response rate. Safety assessments will include evaluations for \geq Grade 3 adverse reactions, all adverse reactions, and serious adverse reactions.

PMR Milestone Dates:
Submit Draft Protocol (3 months before final protocol submission): 04/15 (*based on projected action date*)
Final Protocol Submission: 07/15
Trial Completion: 07/19
Final Clinical Trial Report Submission: 07/20
 - b. **CMC Post-Marketing Commitment:** Submit a prior approval supplement (PAS) with a request to sunset the test and acceptance criterion based on the submitted data with the following information:
 - A limit test for level (b)(4) of the drug substance in the drug product including the analytical method and its validation.
 - Supporting data for the limits.PMC Milestone Date:
PAS Submission: 06/15
3. **Major labeling issues** – 30 minutes
4. **Review Plans** – 5 minutes
 - Conclude labeling negotiations
 - Conclude manufacturing facility inspections
 - Estimated action date late February
5. **Wrap-up and Action Items** – 5 minutes

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/s/

PATRICIA KEEGAN
01/22/2015