

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201532

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 201532/0

SUPPL #

HFD # 107

Trade Name Halaven

Generic Name Eribulin Mesylate Injection

Applicant Name Eisai, Incorporated

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

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

YES

NO

If yes, explain:

=====

Name of person completing form: Vaishali Jarral

Title: Regulatory Project Manager

Date: 8/9/10

Name of Office/Division Director signing form: Dr. Patricia Keegan

Title: Division Director

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/16/2010

PATRICIA KEEGAN
08/25/2010

Pediatric Research and Equity Act Waivers

IND/NDA/BLA #: 102532/0

Supplement Type: n/a

Supplement Number: n/a

Product name and active ingredient/dosage form: Eribulin Mesylate, Injection, 0.5mg/mL (1.0 mg/2mL solution)

Sponsor: Eisai Inc.

Indications(s): For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. 0 to 18
2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):
 - a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I ✓
 - b. The product would be ineffective or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. Suggested language includes, “FDA has not required pediatric studies in ages 0 to 18 because (state the safety or effectiveness reason).”
 - c. The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - d. Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this report submitted by the Sponsor will be publicly posted.

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis

Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:

Basal cell
Bladder

Breast✓
Cervical
Colorectal
Endometrial
Gastric
Hairy cell leukemia
Lung (small & non-small cell)
Multiple myeloma
Oropharynx (squamous cell)
Ovarian (non-germ cell)
Pancreatic
Prostate
Renal cell
Uterine

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

/s/

VAISHALI JARRAL
10/25/2010



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

Memorandum

Date: October 1, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: NDA 201532/0
ONDQA PMC negotiation with the sponsor

From: Jarral, Vaishali
Sent: Friday, October 01, 2010 1:22 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: NDA 201532- Additional Post Marketing Commitment

Ms. Petraglia,

Please see below the agency's additional communication regarding Post marketing commitments. Please let me know if you have any concerns or objection by October 5, 2010.

Post Marketing Commitment (PMC):

Synthesizing the enantiomers of (b) (4), and to developing analytical methods and acceptance criteria (NMT (b) (4)) specific to each enantiomer.

Regarding starting material (b) (4), and revised intermediates (b) (4)

- * Develop analytical method(s) for other specified, unspecified and total impurities.
- * Develop an acceptance criterion for other specified, unspecified and total impurities with appropriate justification.

Develop an identification test for intermediate (b) (4)

Evaluation the specificity of the current identification method for (b) (4) and, if necessary, develop a more selective method.

For the diastereomers of (b) (4):

- * Develop a selective identification method for (b) (4)
- * Evaluate the selectivity of the current identification method for (b) (4) and, if necessary, develop a more selective method.
- * Develop a more selective methods for identification and purity of the diastereomers of (b) (4)

This information and data will be submitted in a single prior approval Chemistry, Manufacturing and Controls supplement to the NDA by 31 March 2011.
Please confirm the receipt of this email.

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/07/2010



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

Memorandum

Date: October 17, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Carton and Container Labeling Discussion with Eisai Inc.

From: "Jarral, Vaishali" <Vaishali.Jarral@fda.hhs.gov>
To: "Jarral, Vaishali" <Vaishali.Jarral@fda.hhs.gov>, "Annmarie_Petraglia@Eisai.com" <Annmarie_Petraglia@Eisai.com>
Date: 10/17/2010 11:25 PM
Subject: RE: Halaven Carton and Label Revisions-NDA 20,1532

Ms. Petraglia,

Regarding Carton and Container, please see the following comment:

Please accommodate the full address, or at a minimum, the city, state and zip code in the carton labeling for manufacturer and distributor. We acknowledge that it might be hard to do so for the container (vial) label.

Please let me know if that is possible. Thank you and please call me if you have any concerns.

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/28/2010



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

Memorandum

Date: October 17, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Labeling Discussion with Eisai Inc.

From: Jarral, Vaishali
Sent: Monday, October 18, 2010 4:35 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Halaven Label (PI and PPI)- NDA 201532

Ms. Petraglia,

Please see attached the FDA's edits and comments to the Halaven Label (PI & PPI) in response to Eisai's edits/comments submitted to FDA on 9/30/2010.



Halaven HALAVEN_10-18-10
_101810_TO_Eisai.d _to_Eisai.doc ...

Please send me your revised comments/edits to this PI & PPI by October 21, 2010. Also, when you submit the final label to the NDA, please attach the patient package insert with the PI. Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

12 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Law Enforcement Action (b7)

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

/s/

VAISHALI JARRAL
10/27/2010

eCTD NDA 201532/0
Eribulin Mesylate
Industry Meeting
10-20-10
Memorandum

Date: October 20, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Teleconference with SGE, Debra Madden: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Halaven (eribulin mesylate) Injection
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
SGE: Debra Madden.

FDA attendees:

Martha Donoghue, Clinical Reviewer
Steven Lemery, Clinical Reviewer Team Leader
Patricia Keegan, Division Director
Vaishali Jarral, Regulatory Project Manager

Meeting Summary: A teleconference was held with Debra Madden on October 20, 2010 to obtain her expert advice as a patient representative regarding New Drug Application (NDA) 201532, submitted by Eisai, Inc. A briefing document and copy of the proposed label for Halaven (eribulin mesylate) was faxed to Ms. Madden on September 24, 2010 in preparation for this teleconference.

During the teleconference, Ms. Madden affirmed that from her perspective, the improvement in overall survival observed in patients randomized to receive eribulin in Study 305 represents a meaningful benefit to patients with refractory metastatic breast cancer. She had no major concerns regarding approval of this application. Additionally, Ms. Madden recommended a few changes to the proposed label in order to more clearly communicate and mitigate the risks associated with Halaven. FDA described recent changes to the Halaven label and the patient package insert (which Ms. Madden had not had the opportunity to review). Ms. Madden stated that the patient package insert and recent labeling changes described by FDA appeared to address her concerns.

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

/s/

VAISHALI JARRAL
10/25/2010

eCTD NDA 201532/0
Halaven (eribulin mesylate) Injection
Wrap-up Meeting
10-21-10

Date: October 21, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Wrap-up Meeting, NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Halaven (eribulin mesylate) Injection
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated

Following Agenda Items were discussed

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

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

/s/

VAISHALI JARRAL
10/27/2010

eCTD NDA 201532/0
Eribulin Mesylate
Industry Meeting
10-25-10
Memorandum

Date: October 25, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Teleconference with SGE, Dr. Aman Buzdar: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Halaven (eribulin mesylate) Injection
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
SGE: Aman Buzdar, M.D.

FDA attendees:

Martha Donoghue, Clinical Reviewer
Steven Lemery, Clinical Reviewer Team Leader
Patricia Keegan, Division Director
Vaishali Jarral, Regulatory Project Manager
Patricia Cortazar, Clinical Reviewer Team Leader
Tatiana Prowell, Clinical Reviewer

Meeting Summary: A teleconference was held with Dr. Aman Buzdar on October 19, 2010 to obtain his expert advice regarding New Drug Application (NDA) 201532, submitted by Eisai, Inc. A briefing document and copy of the proposed label for Halaven (eribulin mesylate) was faxed to Dr. Wilson on September 27, 2010 in preparation for this teleconference.

During the teleconference, Dr. Buzdar concurred that the improvement in overall survival observed in patients randomized to the eribulin arm in Study 305 represents a meaningful benefit to patients with refractory metastatic breast cancer. He stated that he had no concerns with this application and was comfortable with the approval of Halaven for the proposed indication. Dr. Buzdar also commented that the proposed product labeling was informative and clear.

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

/s/

VAISHALI JARRAL
10/27/2010



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

Memorandum

Date: October 27, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Labeling Discussion with Eisai Inc.

From: Jarral, Vaishali
Sent: Wednesday, October 27, 2010 5:33 PM
To: 'Annmarie_Petraglia@Eisai.com'
Cc: Chaudhry, Danyal
Subject: Labeling discussion- NDA 201532

Ms. Petraglia,

Please see attached the FDA's edit and comment to the Halaven Label (PI) in response to Eisai's edits/comments submitted to FDA on 10/22/10.



HALAVEN
10-20-10 (FDA).doc

Please send me your revised comments/edits to this PI by October 29th (if possible) or by early November 1, 2010. Please submit it to the NDA as well. Also note that when you submit the final label to the NDA, please attach the patient package insert with the PI.

Please make sure that you include Danyal Chaudhry in all your emails.

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/28/2010



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

Memorandum

Date: October 28, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Labeling Discussion with Eisai Inc.

From: Jarral, Vaishali
Sent: Thursday, October 28, 2010 4:32 PM
To: 'Annmarie_Petraglia@Eisai.com'
Cc: Chaudhry, Danyal
Subject: RE: Labeling discussion- NDA 201532 URGENT

Response from FDA regarding your email below is:

"You are correct that the number is not 54. However, the number should be revised to 5 based on the updated study report that you submitted in response to an information request from FDA. Your submission is attached and includes the information regarding the additional patient enrolled in the Child-Pugh B group (page 11, Table 1)."

Please let me know if agree with this change and if you do, please email me the final version of the PI and also submit the final label to the NDA 201532.

Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/28/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: October 5, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #7 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.
Agenda: Reviewed Eisai's comments to the label, corrected formatting issues, and discussed comments related to the review of the eribulin label.

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

/s/

VAISHALI JARRAL
10/12/2010



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

Memorandum

Date: October 7, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request Carton and Container Label to Eisai

From: Jarral, Vaishali
Sent: Friday, October 08, 2010 12:02 AM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Carton and container label- NDA 201532

Ms. Petraglia,

FDA is requesting the following changes to the carton and container labels:

1. Capitalize the first letter of the dosage form ("Injection") as it is part of the name. - Halaven (eribulin mesylate) **I**njection.
2. Display manufacturer/distributor information consistently on all the labels (PI, carton and container) to prevent any potential confusion.

Please provide the revisions by October 13, 2010 and confirm the receipt of this email.

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/12/2010



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

Memorandum

Date: October 7, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
PMR Discussion with Eisai Inc.

From: Jarral, Vaishali
Sent: Thursday, October 07, 2010 2:58 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Post-action feedback meeting

Ms. Petraglia,

Please see the attached "Quality assessment check list" that was sent to you with the acknowledgement letter. Please see the purpose statement for this checklist. Post-action feedback meeting is a feedback or lessons learned meeting.

FDA does not require this meeting, but the option is there for you if you need to have this meeting.

This meeting is intended to discuss the process including quality of the application and communication. It is not intended to address scientific issues or approvability requirements. The meeting should focus on those items that provide lessons learned (i.e., things that worked well and things that did not) for future applications.



Quality_assessment
.doc (153 KB...)

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

/s/

VAISHALI JARRAL
10/27/2010

eCTD NDA 201532/0
Eribulin Mesylate
Industry Meeting
10-19-20
Memorandum

Date: October 19, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Teleconference with SGE, Dr. Wyndham Wilson: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Halaven (eribulin mesylate) Injection
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
SGE: Wyndham Wilson, M.D.

FDA attendees:

Martha Donoghue, Clinical Reviewer
Steven Lemery, Clinical Reviewer Team Leader
Patricia Keegan, Division Director
Vaishali Jarral, Regulatory Project Manager

Meeting Summary: A teleconference was held with Dr. Wyndham Wilson on October 19, 2010 to obtain his expert advice regarding New Drug Application (NDA) 201532, submitted by Eisai, Inc. A briefing document and copy of the proposed label for Halaven (eribulin mesylate) was faxed to Dr. Wilson on September 22, 2010 in preparation for this teleconference.

During the teleconference, Dr. Wilson stated that the improvement in overall survival observed in patients randomized to the eribulin arm in Study 305 appears to represent a clinical benefit that has supported approvals in the past. Overall, he had no major concerns regarding the approvability of this application. Dr. Wilson had no other comments regarding product labeling.

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

/s/

VAISHALI JARRAL
10/25/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting Agenda
9-30-10
Memorandum

Date: September 30, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #9 Agenda: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Team meeting was held to discuss the CMC related issues/deadlines; PMR/PMC/Labeling negotiations issues/timeline and to discuss the status of pending reviews.

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

/s/

VAISHALI JARRAL
10/12/2010

The following email was sent to Dr. Aman Buzdar (SGE) on September 27, 2010.

From: Jarral, Vaishali
Sent: Monday, September 27, 2010 2:18 PM
To: 'abuzdar@mdanderson.org'
Subject: FDA Correspondence (Teleconference- October 21, 2010)
Importance: High
Sensitivity: Confidential

Dr. Buzdar,

As you have confirmed that the most secure way to send you the documents related to NDA application 201532 is via email, please see the attached documents.

Enclosed you will find the following:

- 1) Cover Letter
- 2) Timekeeper payroll record
- 2) Summary of the single randomized trial submitted with this application (study 305)
- 3) Proposed eribulin product labeling

Please note that the material in this email is highly confidential.



Coverletter(Dr-Buz Timekeeper Payroll 11 August 2010 Erisai_LabelEribulin-S
dar).pdf (27... Record.doc ... Briefing Docume... GE.pdf (2...

Please confirm the receipt of this email.

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248



Dear Dr. Buzdar,

Thank you for agreeing to provide advice regarding New Drug Application (NDA) 201532, submitted by Eisai Pharmaceuticals. Please note that information concerning this application is confidential.

In this application, the sponsor seeks approval of a first-in-class, new molecular entity, eribulin mesylate, for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapy regimens, including an anthracycline and a taxane.

Enclosed is a timekeeper payroll record, summary of the single randomized trial submitted with this application (Study 305), and the proposed eribulin product labeling for your review.

Agenda: As we discussed during our recent conversation, we will have a teleconference to discuss this application and seek advice regarding the following questions:

1. Does the 75 day improvement in median overall survival achieved by patients treated with eribulin mesylate in Study 305 represent a clinically meaningful benefit?
2. Based upon the data in this study, does the risk/benefit ratio favor treating patients with refractory metastatic breast cancer with eribulin?
3. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of eribulin treatment?

Details regarding the Teleconference:

Time: October 21 (Thursday), 2010 1:30 PM to 2:00 PM (EST)

Call-in number: 1-877-954-4889

Pass code: 1285833

Thank you again for your time and insights.

Sincerely,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

TIMEKEEPER PAYROLL RECORD

Advisors and Consultants Staff

Note to Center for Drug Evaluation and Research Special Government Employee.

Use this record to submit claim for hours worked at your home, place of business, or in any FDA facility located within your commuting area. Please note any dates that you were required to travel outside of your commuting area to perform your assignment. Advisory committee members should not claim salary for hours spent on normal preparation for a committee meeting. Salary paid in response to this time sheet represents compensation in full for all services rendered and supplied by the Special Government Employee during this period.

Date(s) Hours Worked Description of Work
(Cite IND/NDA if applicable)

_____ (Sign) _____
Special Government Employee Date

Certification:

I certify that this work was done during the period(s) indicated at:

- Government furnished facility
- Employees home/office since there was no Federal office or laboratory space available at which to perform the assigned work.
- Quality and quantity of work meets performance expectations.

_____ Date
Center for Drug Evaluation and Research Executive
Secretary/Management Official Authorizing Assignment

Briefing Document for FDA Teleconference to Discuss NDA 201532
Eribulin Mesylate, Injection
Eisai Pharmaceuticals

Introduction

- On March 30, 2010, Eisai Pharmaceuticals submitted NDA 201532 seeking approval of eribulin mesylate for the treatment of (b) (4) metastatic breast cancer.
- Eribulin is a new molecular entity that is a synthetic analog of Halichondrin B, derived from the marine sponge *Halichondria okadai*.
- Eribulin exerts cytotoxic activity by inhibiting the growth phase of microtubules and sequestering tubulin into nonfunctional aggregates.
- During the course of clinical development, eribulin has been administered to a total of 1,222 patients, including 827 patients with breast cancer.
- NDA 201532 includes data from a single randomized clinical trial, Study 305.

Design of Study 305

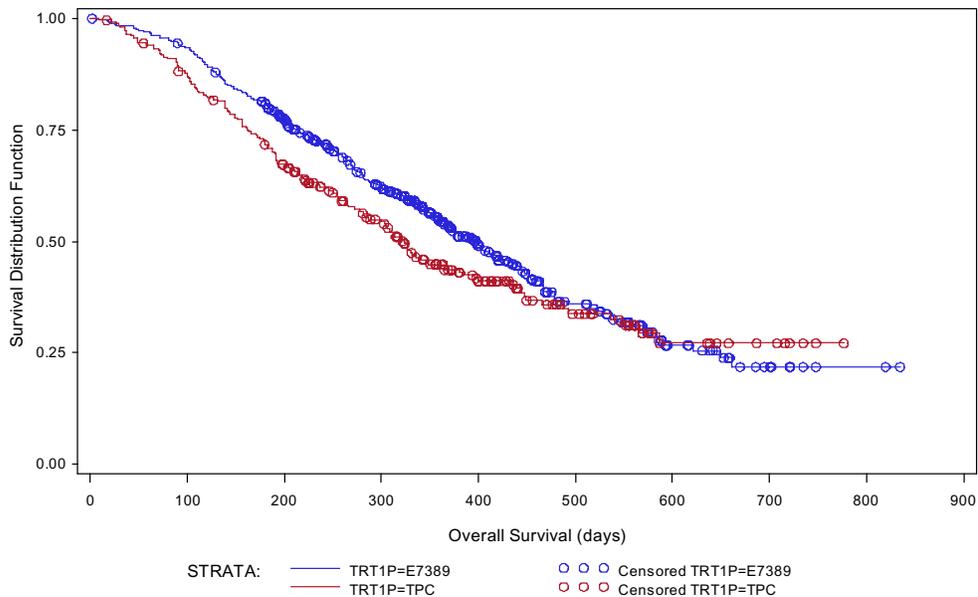
- Study 305 is an open label, randomized multicenter, international study comparing eribulin to a “Treatment of Physician’s Choice” (TPC) in patients with refractory metastatic breast cancer.
- In this study, 762 patients were randomized on a 2:1 basis to receive either eribulin or TPC (a single-drug regimen chosen by the physician for each patient prior to randomization).
 - Patients were stratified by HER2 status, prior capecitabine exposure, and geographical region.
 - TPC therapy could include any cytotoxic, biological, or hormonal therapy.
 - Primary endpoint was overall survival (OS), with secondary endpoints of progression-free survival (PFS) and objective response rate (ORR).
 - The analysis was pre-specified to occur after 411 enrolled patients died (representing 55% of the total number of patients).
- Patients were required to meet the following key eligibility criteria for enrollment:
 - 2-5 prior chemotherapy regimens
 - At least 2 regimens in the metastatic or locally recurrent setting
 - At least one prior anthracycline and taxane
 - Refractory to most recent chemotherapy regimen.

Briefing Document for FDA Teleconference to Discuss NDA 201532
Eribulin Mesylate, Injection
Eisai Pharmaceuticals

Results of Study 305

- Baseline characteristics of enrolled patients were comparable between treatment arms:
 - Median age: 65 years
 - 92% White
 - 64% enrolled in North America, Western Europe, or Australia (19% of total patients were enrolled in the United States)
 - 67% of patients were estrogen receptor positive, 49% of patients were progesterone receptor positive, and 16% of patients were HER2 positive
 - 83% of HER2 positive patients received HER2-directed therapy prior to enrollment
 - 19% of patients had triple negative status
 - 82% had visceral disease
 - Patient received a median of 4 prior chemotherapy regimens
 - 73% of patients had received capecitabine prior to enrollment
 - Two patients had disease that was locoregional only.
- For the 254 patients randomized to the TPC arm, 26% of patients received vinorelbine, 18% of patients received gemcitabine, 18% received capecitabine, 16% received a taxane, and 9% received an anthracycline. A total of 10% of patients received another type of chemotherapy, and 3% received hormonal therapy.

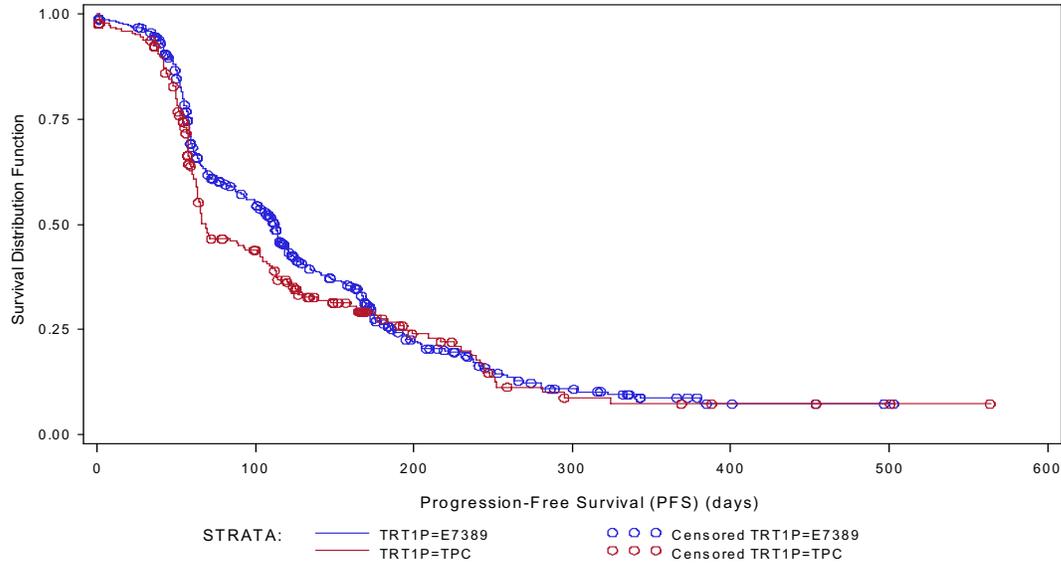
Kaplan-Meier Curve for Prespecified Analysis of Overall Survival Reflecting Data after 422 Deaths (ITT Population)



HR: 0.81 (0.66, 0.99); p-value: 0.041. Median OS for Eribulin: 399 days; Median OS for TPC: 324 days (a 75-day difference in median OS).

**Briefing Document for FDA Teleconference to Discuss NDA 201532
Eribulin Mesylate, Injection
Eisai Pharmaceuticals**

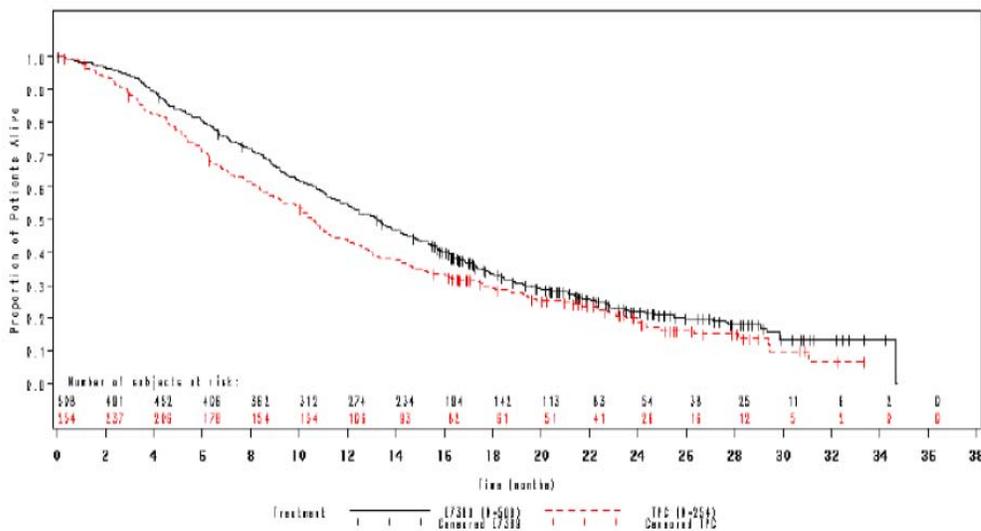
Kaplan-Meier Curve for Progression-Free Survival by Independent Review
(ITT Population)



HR: 0.865 (0.71, 1.048); p-value: 0.137. After 521 PFS events, median PFS for eribulin was 113 days versus 68 days for the TPC group (a 45-day difference).

- The sponsor conducted an additional post-hoc analysis of overall survival after 589 deaths (77% of enrolled patients).

Kaplan-Meier Analysis of OS Using Updated Data Based Upon a Request from EMA
(eribulin arm is indicated in black):



HR: 0.805 (0.667, 0.958)

Briefing Document for FDA Teleconference to Discuss NDA 201532
Eribulin Mesylate, Injection
Eisai Pharmaceuticals

Additional Supportive Analyses of Efficacy

- PFS analysis conducted using investigator assessment of progression (635 events versus 521 events using the IRC analysis) favored the eribulin arm [HR:0.757 (0.638, 0.900); p=.002]
- ORR was 11.2% in the Eribulin Arm (54 partial responses and 3 complete responses) and 3.9% in the TPC arm (all partial responses) (p=0.0006).
- The sponsor submitted supportive data from two single arm studies of eribulin in patients with metastatic breast cancer that demonstrated response rates of 9.3% (95% CI: 6.2, 13.2) and 13.6% (95% CI: 7.6, 21, 8) by independent review.

Analysis of Safety Data from Study 305

- The overall toxicity profile of eribulin appears similar to that of other approved agents that disrupt microtubule dynamics, such as the taxanes and vinca alkaloids (i.e., common toxicities include neutropenia and peripheral neuropathy).
- Eribulin-treated patients completed a median of 5 cycles of therapy, compared to 3 cycles in the TPC group.
- 55% of eribulin-treated patients required dose delays or interruptions at some point during therapy, and 29% required dose reductions (mostly for neutropenia-related adverse events)
 - Neutropenia was the most common adverse event leading to dose adjustment
- Treatment emergent adverse events occurred in 99% of patients treated in the eribulin group, compared to 93% of patients receiving TPC therapy
- 25% of patients in both arms experienced serious adverse events (SAE)
 - The most common SAE in the eribulin group was febrile neutropenia (4% of patients).
- Grade 3 or 4 treatment emergent adverse events occurred in 68% of eribulin-treated patients and 54% of TPC patients
- Adverse events occurring in at least 20% of eribulin-treated patients:
 - Asthenic and fatigue (54%)
 - Neutropenia (52%)
 - Alopecia (45%)
 - Peripheral neuropathy (36%)
 - Nausea (35%)
 - Constipation (25%)
 - Arthralgia/myalgia (22%)
 - Decreased weight (21%), Anorexia (20%)
 - Pyrexia (21%)
- 5% of patients discontinued eribulin due to peripheral neuropathy

12 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Law Enforcement Action (b7)

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

/s/

VAISHALI JARRAL
09/28/2010



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

Memorandum

Date: September 24, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request Carton and Container Label to Eisai

From: Jarral, Vaishali
Sent: Friday, September 24, 2010 10:31 AM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Additional comments for the revised container and carton label- NDA 201532

Ms. Petraglia,

FDA has the following comments on the revised container label and carton labeling submitted by Eisai, Inc on September 20, 2010:

Container Label

The "Rx only" statement is too prominent on the label. Relocate the "Rx only" statement to a less prominent area on the label (e.g., to the right of the NDC number) and decrease the font weight.

Carton Labeling

The tri-circular graphic located next to the proprietary name is in too close proximity to the name and distracts from the readability of the name. Please move the graphic to an area that is not in too close proximity to the proprietary name (e.g., a little further to the left of the proprietary name).

Please submit the revised Carton and Container label to the NDA and to me via email by September 30, 2010. Thank you.

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/07/2010



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

Memorandum

Date: September 22, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
PMR Discussion with Eisai Inc.

From: Jarral, Vaishali
Sent: Wednesday, September 22, 2010 1:19 PM
To: 'Annmarie_Petraglia@Eisai.com'
Cc: Sheila_Talatala@Eisai.com
Subject: RE: NDA 201532- Information Request-NCI Study -patients with severe renal impairment.

Ms. Petraglia,

In response to your email below:

"The available data is inadequate to address the PMR. Eisai should assess and modify the timeline proposed by the Agency with the intention of conducting a dedicated PK trial for patients with severe renal impairment (defined as a CrCl < 30 ml/min) and for patients with normal renal function."

Thank you,

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

From: Annmarie_Petraglia@Eisai.com [mailto:Annmarie_Petraglia@Eisai.com]
Sent: Friday, September 17, 2010 1:22 PM
To: Jarral, Vaishali
Subject: Re: NDA 201532- Information Request-NCI Study -patients with severe renal impairment.

Dear Vaishali,

We have contacted NCI to obtain the information you requested in your e-mail of 9-14-2010. We have confirmed there are 4 patients with severe renal impairment [creatinine clearance < 30mL/min.] However, the data are being reviewed to determine if there are additional patients with the creatinine level required.

I hope to provide a more complete answer by next week.

Regards,
Annmarie

Annmarie Petraglia
Senior Director, Regulatory Affairs-Oncology
Eisai Medical Research Inc.
300 Tice Blvd.
Woodcliff Lake, N.J. 07677
Direct:201-949-4516
e-mail:annmarie_petraglia@eisai.com

From: "Jarral, Vaishali" <Vaishali.Jarral@fda.hhs.gov>
To: "Annmarie_Petraglia@Eisai.com" <Annmarie_Petraglia@Eisai.com>
Date: 09/14/2010 11:08 AM
Subject: NDA 201532- Information Request

Ms. Petraglia,

Regarding the PMR for renal impairment study under NDA 201-532 Eribulin mesylate (Halaven):
Indicate the number of patients included in this NCI phase I/II trial that have severe renal impairment
(creatinine clearance < 30 mL/min) with adequate eribulin PK data available, and when the final report
can be submitted. Provide your response by this Friday, September 17, 2010. The Agency will determine
whether the available data can adequately address the PMR and modify the PMR accordingly.

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/27/2010



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

Memorandum

Date: September 22, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
PMR/PMCs negotiation with the sponsor initiated on September 7, 2010 and revised PMC was sent to Eisai on September 20, 2010.

From: Jarral, Vaishali
Sent: Wednesday, September 22, 2010 1:19 PM
To: 'Annmarie_Petraglia@Eisai.com'
Cc: Sheila_Talatala@Eisai.com
Subject: RE: NDA 201532- Information Request-NCI Study -patients with severe renal impairment.

Ms. Petraglia,

In response to your email below:

"The available data is inadequate to address the PMR. Eisai should assess and modify the timeline proposed by the Agency with the intention of conducting a dedicated PK trial for patients with severe renal impairment (defined as a CrCl < 30 ml/min) and for patients with normal renal function."

Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

From: Annmarie_Petraglia@Eisai.com [mailto:Annmarie_Petraglia@Eisai.com]
Sent: Friday, September 17, 2010 1:22 PM
To: Jarral, Vaishali
Subject: Re: NDA 201532- Information Request-NCI Study -patients with severe renal impairment.

Dear Vaishali,

We have contacted NCI to obtain the information you requested in your e-mail of 9-14-2010. We have confirmed there are 4 patients with severe renal impairment [creatinine clearance < 30mL/min.] However, the data are being reviewed to determine if there are additional patients with the creatinine level required.

I hope to provide a more complete answer by next week.

Regards,
Annmarie

Annmarie Petraglia
Senior Director, Regulatory Affairs-Oncology
Eisai Medical Research Inc.
300 Tice Blvd.
Woodcliff Lake, N.J. 07677
Direct:201-949-4516
e-mail:annmarie_petraglia@eisai.com

From: "Jarral, Vaishali" <Vaishali.Jarral@fda.hhs.gov>
To: "Annmarie_Petraglia@Eisai.com" <Annmarie_Petraglia@Eisai.com>
Date: 09/14/2010 11:08 AM
Subject: NDA 201532- Information Request

Ms. Petraglia,

Regarding the PMR for renal impairment study under NDA 201-532 Eribulin mesylate (Halaven):

Indicate the number of patients included in this NCI phase I/II trial that have severe renal impairment (creatinine clearance < 30 mL/min) with adequate eribulin PK data available, and when the final report can be submitted. Provide your response by this Friday, September 17, 2010. The Agency will determine whether the available data can adequately address the PMR and modify the PMR accordingly.

Thank you,

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

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

/s/

VAISHALI JARRAL
10/07/2010



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

Memorandum

Date: September 21, 2010

From: Vaishali Jarral, Regulatory Project Manager

Subject: *NDA 201532/0*

Labeling negotiation with the sponsor initiated on September 21, 2010

From: Jarral, Vaishali
Sent: Tuesday, September 21, 2010 5:48 PM
To: 'Annmarie_Petraglia@Eisai.com'; Sheila_Talatala@Eisai.com
Subject: NDA 201532-FDA revised Label and Patient Package Insert- Halaven (Eribulin Mesylate)

Hello,

Good Afternoon Ladies,

Please find attached a revised version of the label and the patient package insert for NDA 201532. These documents contain the Agency's changes to the label and PPI. Kindly let me know by Tuesday, September 28, 2010, if you have any suggested edits or comments for this version of the label. Also submit your proposed revisions to the NDA (if any).



Eisai_LabelEribulin.d NDA201532-
oc (860 K... 'PI_Eisai.doc (96 K..

Please note that the label is still under review and this is not a final version.

Please confirm the receipt of this email.

Thank you,
Vaishali

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

/s/

VAISHALI JARRAL
09/22/2010



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

Memorandum

Date: September 20, 2010

From: Vaishali Jarral, Regulatory Project Manager

Subject: *NDA 201532/0*

PMR/PMCs negotiation with the sponsor initiated on September 7, 2010 and revised PMC was sent to Eisai on September 20, 2010.

From: Jarral, Vaishali
Sent: Monday, September 20, 2010 3:56 PM
To: 'Annmarie_Petraglia@Eisai.com'; Sheila_Talatala@Eisai.com
Subject: Revised PMC #2- NDA 201532

Hello Ms. Petraglia,

Please find attached the agency's communication regarding revised Post marketing commitment #2. Reason for the revision: "The agency is requesting a subset analysis for the population of patients that progressed while on a taxane or other microtubule inhibiting agent in order to better assess the efficacy of Halaven in this patient population."

Please note that we may have additional post marketing/commitments that would be communicated to you at the later date.

We are requesting a turn around time of 4 days (September 24, 2010). In your response please indicate if you agree with the revised proposed commitment and the associated milestones/timepoints.



NDA201532_Halaven_Revised_PMC....

In addition, as you proposed the following alternative timeline for the submission of the final study report of the ongoing clinical trial E7389-G000-301 (PMC #2):

"Trial Completion date :March 2012
Final Report Submission: February 2013"

The agency agrees to the change in dates. Please see the attached document for more details.

Thank you,

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

Attachment
Draft Erubilin
Post Marketing Requirements (PMR)/Post Marketing Commitments (PMC)

Revised PMC 2

To submit a final study report for ongoing trial E7389-G000-301, “A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes.” This study report will include a subset analysis of overall survival in patients that progressed while on treatment with a taxane or other microtubule inhibiting agent. The original protocol for clinical trial E7389-G000-301 was submitted to FDA on November 17, 2005, and began patient accrual on September 20, 2006. We also acknowledge receipt of the protocol amendments received on December 14, 2005; March 2, 2006; May 11, 2006; December 5, 2006; October 31, 2007; March 6, 2008; and March 3, 2009.

The FDA is proposing that you conduct the trial according to the following milestones or propose alternative timelines that will be acceptable to the FDA:

Trial Completion Date:
Final Report Submission:

March 2012
February 2013.

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

/s/

VAISHALI JARRAL
09/22/2010



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

Memorandum

Date: September 14, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request Carton and Container Label to Eisai

From: Jarral, Vaishali
Sent: Tuesday, September 14, 2010 2:04 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: NDA 201532- Carton and Container Label

Hello Ms. Petraglia,

Please see attached the list of comments from FDA regarding Carton and Container label for NDA 201532.

Comments:

A. Container Label and Carton Labeling

1. As currently presented, the Eribulin established name is difficult to read because of the type of font and the font weight used. Ensure the established name is at least ½ the size of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
2. Present the route of administration statement in title case (i.e., “For Intravenous Use”).

B. Carton Labeling

1. The principal display panel appears crowded because it contains duplicative information that is found on the rear panel. The principal display panel is used by healthcare professionals to identify the drug. Thus, we have the following recommendations.
 - a. Delete the following statements from the principal display panel since this information is already present on the back panel: 1) “Each vial contains...” statement 2) Dosage and Use statement 3) Storage conditions statement.
 - b. Align the statement of strength with the left margin of the proprietary name and established name as was done on the container label.
 - c. Relocate the statements “Sterile Solution” and “Caution: Cytotoxic Agent” to the area below the route of administration.
2. Increase the prominence of the statement “Single use vial—discard unused portion.”

Please incorporate these changes to the carton and container labels and send me the mock-up of the container label and the carton labeling that shows the proposed trade dress and the recommended changes by September 20, 2010. Please provide the information requested as an amendment to the NDA as well.

Please confirm the receipt of this email.

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
09/22/2010



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

Memorandum

Date: September 14, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
PMR Discussion with Eisai Inc.

From: Jarral, Vaishali
Sent: Tuesday, September 14, 2010 11:08 AM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: NDA 201532- Information Request

Ms. Petraglia,

Regarding the PMR for renal impairment study under NDA 201-532 Eribulin mesylate (Halaven):

Indicate the number of patients included in this NCI phase I/II trial that have severe renal impairment (creatinine clearance < 30 mL/min) with adequate eribulin PK data available, and when the final report can be submitted. Provide your response by this Friday, September 17, 2010. The Agency will determine whether the available data can adequately address the PMR and modify the PMR accordingly.

Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

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

/s/

VAISHALI JARRAL
10/27/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: September 7, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #6 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.
Agenda: Provided final edits to the label, corrected formatting issues, and discussed any final comments related to the review of the eribulin label.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010



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

Memorandum

Date: September 7, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
PMR/PMCs negotiation with the sponsor initiated on September 7, 2010

From: Jarral, Vaishali
Sent: Tuesday, September 07, 2010 4:32 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: NDA 201532- Halaven (PMR/PMCs)

Ms. Petraglia,

Find attached the agency's communication regarding Post marketing requirements/commitments. Please note that we may have additional post marketing/commitments that would be communicated to you at the later date.

We are requesting a turn around time of one week for these PMR/PMCs (due by September 14, 2010).

In your response please indicate if you agree with the proposed requirements and commitments and the associated milestones/timepoints.



NDA201532_Halave
n.doc (47 KB)

Please confirm receipt of this email.

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Draft Erubilin
Post Marketing Requirements (PMR)/Post Marketing Commitments
(PMC)

Clinical PMRs

PMR 1

To conduct a dedicated renal function clinical trial in accordance with FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling. The "full" study design may be modified to include subjects with normal renal function and subjects with severe renal impairment. The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care consistent with the study population enrolled into the hepatic impairment trial (study 108). The renal function groups should be balanced with respect to age, gender and weight. The number of patients enrolled in the study should be sufficient to detect PK differences to warrant dosage adjustment recommendation. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan will be included in the final protocol submitted to FDA.

The FDA is proposing that you conduct the trial according to the following milestones or propose alternative timelines that will be acceptable to the FDA:

Final Protocol Submission:	12/31/2010
Trial Completion Date:	06/30/2012
Final Report Submission:	12/31/2012

Clinical PMCs

PMC 1

To submit a final report that includes updated results for overall survival and datasets for overall survival for trial E7389-G000-305, "A Phase 3 Open Label, Randomized Parallel Two-Arm Multi-Center Study of E7389 versus 'Treatment of Physician's Choice' in Patients with Locally Recurrent or Metastatic Breast Cancer, Previously Treated with At Least Two and a Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane" after 95% of patient deaths have occurred (724 deaths in 762 enrolled patients).

The original protocol for clinical trial E7389-G000-305 was submitted to FDA on April 26, 2006, and began patient accrual on November 16, 2006. We also acknowledge receipt of the protocol amendments received on August 8, 2006; January 4, 2008; June 5, 2008; and March 3, 2009.

The FDA is proposing that you conduct the trial according to the following milestones or propose alternative timelines that will be acceptable to the FDA:
Final Report Submission: March 1, 2013.

PMC 2

To submit a final study report for ongoing trial E7389-G000-301, "A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes." The original protocol for clinical trial E7389-G000-301 was submitted to FDA on November 17, 2005, and began patient accrual on September 20, 2006. We also acknowledge receipt of the protocol amendments received on December 14, 2005; March 2, 2006; May 11, 2006; December 5, 2006; October 31, 2007; March 6, 2008; and March 3, 2009.

The FDA is proposing that you conduct the trial according to the following milestones or propose alternative timelines that will be acceptable to the FDA:

Trial Completion Date: March 2011
Final Report Submission: February 2012.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/08/2010



NDA 201532

MEETING MINUTES

Eisai Inc.
Attention: Monica Lee, Director
Regulatory Affairs-CMC
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Lee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eribulin mesylate, Injection, 0.5 mg/mL (1.0 mg/2 mL solution).

We also refer to the meeting between representatives of your firm and the FDA on 02 Jul 2010. The purpose of the meeting was to discuss with the FDA on the GMP starting materials for the synthesis of eribulin mesylate.

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

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Chemistry, Manufacturing and Controls (CMC) Guidance Meeting

Meeting Date and Time: Friday, 2 Jul 2010, 1100 – 1200 ET
Meeting Location: Food and Drug Administration
White Oak Campus, Silver Spring, MD

Application Number: NDA 201532
Product Name: Eribulin Mesylate Injection
Indication: Proposed for the treatment of patients with locally advanced or metastatic breast cancer whose disease has progressed after already receiving 2 or more previous chemo regimens, including an anthracycline and a taxane

Sponsor/Applicant Name: Eisai Medical Research, Inc. (Eisai)

Meeting Chair: Richard T. Lostritto, PhD
Meeting Recorder: Scott N. Goldie, PhD

FDA ATTENDEES

William M. Adams, Branch Chief (*Acting*)
Josephine M. Jee, PhD, Product Quality Reviewer
Scott N. Goldie, PhD, Product Quality Regulatory Project Manager
Julia Lee, Pharmacy Student, University of Maryland, School of Pharmacy
Richard T. Lostritto, PhD, Division Director
Ying Wang, PhD, Product Quality Reviewer
Liang Zhou, PhD, CMC Lead

SPONSOR ATTENDEES

Robert Costanzo - Director, Quality Control
Frank Fang - Vice President, US API Process Development
Adam Grobin - Exec. Director, Analytical Development
Takashi Hasebe - Senior Scientist, Analytical Chemistry
Monica Lee - Director, Regulatory-CMC
Bryan Lewis - Senior Director, Global Project Management
Michael Lewis - President, Pharmaceutical Sciences & Technology
John Orr - Director, Analytical Chemistry
Katsuya Tagami - Senior Director, API Research, CMC Japan
Mark Taisey - President, Global Regulatory Affairs
Nicholas Tamasco - Executive Director, Global Quality Assurance
Gordon Wilkie - Senior Research Investigator, Process Research

1.0 BACKGROUND

Eisai submitted NDA 201532 on 30 Mar 2010 for eribulin mesylate injection proposed for the treatment of patients with locally advanced or metastatic breast cancer whose disease has progressed after already receiving two or more previous chemotherapeutic regimens, including an anthracycline and a taxane. The drug product is a single-use vial of a sterile, ready-to-use, clear/colorless aqueous solution of 0.5 mg/mL in ethanol/water (5:95) intended for administration as a bolus injection or IV infusion in normal saline over 1-60 minutes.

NDA 201532 refers to IND 67193 for E7389 (eribulin mesylate) injection. Chemistry, Manufacturing and Controls (CMC) discussions regarding eribulin mesylate were held on 14 Apr 2006. During this CMC meeting, the acceptability of Eisai's proposed starting materials were discussed. The following is taken from the meeting minutes received by Eisai on 3 May 2006 and included in the NDA (eCTD 1.6.3, p 152):

Question 1: Does the Agency agree with the Eisai proposed starting materials, (b) (4) for the GMP synthesis of E7389?

FDA Response:

1. No. The proposed starting materials, (b) (4) are not acceptable. The selection of starting materials (b) (4)

Minimally, the proposal and justification of starting materials should include the following components:

An unequivocal identity test.

A detailed synthetic scheme.

A thorough discussion of potential (b) (4) of impurities that are present in the starting materials to the final drug substance;

Impurity profile comparison(s) of the proposed starting material(s), as manufactured by different manufacturers;

Appropriate controls of the proposed starting materials using validated analytical test methods to separate and measure potential impurities;

Full supplier information from the intended vendors of any proposed starting materials.

Data from purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to desired levels.

Acceptable change control strategies for any potential revisions to the manufacture of the proposed starting material(s), including the proposed procedures for the vendor's reporting of any changes in starting material manufacture to you.

Supportive literature data, as available.

Meeting Discussion 1: (See Slides 1-17 for an overview of the development process) Eisai stated that all 9 FDA bullets had been addressed, and requested additional input from FDA on the proposed starting materials, (b) (4). FDA stated that each bulleted item was intended to act as a guidance, not to identify specific deficiencies in the immediate application. Any additional information pertaining to starting materials, as is suggested by the slides, should be submitted to allow for review and determination of acceptability as starting materials. FDA further stated that early determination of starting materials is key to development and deserves greater dialog. FDA recommended that information of a substantial nature should be submitted for CMC +/- PharmTox meeting. Eisai stated that they don't understand why the starting materials were not found to be acceptable, specifically, (b) (4). FDA stated that (b) (4).

(b) (4) FDA further stated that Eisai could choose to re-propose (b) (4) and provide additional information (as previously stated) justifying their choice. Eisai asked if there was a guidance for selecting starting materials; specifically, a guidance to determine how (b) (4) to choose an acceptable starting material. FDA stated that any material in the manufacturing process may be proposed. If the material is well-characterized, it will be useful in the justification of the selection as a starting material. FDA further stated that it appeared (from the slides) that Eisai was in possession of substantial additional information pertaining to the proposed starting materials, and that it would be helpful if that information were submitted to justify their choice of starting materials. Eisai agreed to discuss the matter further and asked if a meeting would be granted if the additional information was provided. FDA stated that a meeting or teleconference would be granted if justified by the information and questions submitted, e.g., pertaining to temperature, stability, proposed starting materials, etc. A pre-NDA meeting was also suggested as another option. Eisai stated that they had planned a pre-NDA meeting 6 months prior to filing the NDA. Eisai asked if (b) (4) was the reason for not approving their choice of starting materials. FDA stated that several factors impacted the response that Eisai received; foremost was that the information provided in the background package was not sufficient to justify the proposed starting materials.

Eisai asked for clarification as to what was meant by "A detailed synthetic scheme" (see bullet #2, FDA Response, above). FDA reiterated that the bulleted items were intended as a guide to ensure a more complete submission, not as specific deficiencies in the immediate application. FDA stated that, minimally, the synthetic scheme should include all conditions, reagents, and details for each synthetic step.

On 03 Aug 2006, FDA provided Eisai Medical Research, Inc. with a Pre-Meeting response to their question concerning the proposed starting materials contained in a meeting request received on 05 Jul 2006. Eisai contacted FDA via phone and email for clarification of the FDA response. Specifically, Eisai requested confirmation in writing that FDA accepts that Eisai declares (b) (4) proposed starting materials (b) (4) in the NDA to be considered "as the regulatory starting materials from a GMP perspective", provided we file a separate DMF for each of the proposed materials providing details of earlier steps of the synthesis not declared in the NDA itself?

FDA responded as follows (included in the NDA; eCTD 1.6.3 p 175):

While your approach appears to be reasonable, the acceptability of the proposed starting materials will be determined at the time of NDA submission and review. In the NDA, include the following supporting information for each proposed starting material:

- An unequivocal identity test, which also distinguishes all potential stereoisomers in the compound;
- A detailed synthetic scheme;
- A thorough discussion of potential (b) (4) of impurities that are present in the starting material to the final drug substance;
- Impurity profile comparison of the proposed starting material, as manufactured by different manufacturers;
- Appropriate controls of the proposed starting materials using validated analytical test methods to separate and measure potential impurities;
- Full supplier information from the intended vendors of any proposed starting material;
- Data from purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to desired levels;
- Acceptable change control strategies for any potential revision to the manufacture of the proposed starting material, including the proposed procedures for the vendor's reporting of any changes in starting material manufacture to you
- Supportive literature data, as available.

FDA issued advice letters on 13 May 2010 and 09 Jun 2010 containing recommendations regarding the starting materials. Eisai requested an open dialog to discuss the starting materials on 26 May 2010 *via* email. This request was reviewed without comment. Given the priority nature of the review, FDA recommended that instead of an open dialog meeting Eisai respond to the starting material deficiency with an amendment no later than 16 Jun 2010.

Eisai's concerns regarding ONDQA's position on defining the starting materials for eribulin mesylate were summarized through email and verbal communications with the Office of Oncology Drug Products (OODP) on 14 Jun 2010. Eisai requested an opportunity for a dialogue with the ONDQA reviewers regarding the definition of the starting materials. Eisai also informed OODP that Eisai has (b) (4) on the starting materials through (b) (4).” This dialog, in the form of a Type C CMC Guidance meeting was granted *via* email on 23 Jun 2010.

On 26 Jun 2010, Eisai provided an agenda and slides for presentation at the meeting in lieu of a meeting package. This information is recorded in the administrative file (eCTD 1.6.2 sequence 0009 dated 28 June 2010) and reproduced here in Section 5.

The minutes of the meeting held on 02 Jul 2010 are recorded below.

2.0 DISCUSSION

2.1. GMP STARTING MATERIALS

Question 1: Does the FDA agree with Eisai that (b) (4) are acceptable as GMP starting materials for the synthesis of eribulin mesylate?

FDA Response to Question 1: No response was conveyed to Eisai prior to the meeting.

Discussion: FDA referred to the previous discussions, included in Section 1.0 for clarity, to provide a foundation for the discussion regarding the starting materials. FDA indicated that concerns remained regarding the adequate control of impurities during the manufacturing process of the drug substance due to the complexity of the compound. There was also concern that manufacturing process steps (b) (4) starting materials are not regulated and can be changed in the future without regulatory notification. FDA further expressed concerns that the analytical methods for impurities did not include chiral methodologies and that the pharmaceutical development package did not include detailed data from impurity purging studies to demonstrate the capability of the manufacturing process to remove and control the impurities to acceptable levels.

Eisai presented slides 1-27 (Section 5.0) to facilitate the discussion. Meeting participants agreed that the slide presentation increased the understanding and detail of the manufacturing process that was lacking in the NDA.

FDA maintained that the recommended starting materials communicated to Eisai in the advice letter dated 13 May 2010 and 09 Jun 2010 were the proper starting materials for this application. Eisai agreed to adopt FDA's recommendation regarding the starting materials with minor modification. Eisai will send the justification for the minor modification and FDA agreed to the minor modification in principle.

The (b) (4) starting materials recommended by FDA in the above mentioned advice letters are (b) (4)

The (b) (4) modified starting materials proposed by Eisai are (b) (4)

Eisai expressed concerns that there may not be enough time to prepare for all the necessary documentation regarding the new starting materials. FDA proposed staged submission for all necessary documentation to help Eisai meet the timeline.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no other issues requiring further discussion at the time of the conclusion of the meeting.

4.0 ACTION ITEMS

FDA will send an advice letter after the meeting detailing the necessary information for the new starting materials to facilitate further review of this application. This letter would also list the information needed now for the approval of the application and information that can be submitted post approval.

Eisai committed to provide the information requested in the advice letter in a timely manner.

5.0 ATTACHMENTS AND HANDOUTS

The attached slides were distributed and presented to the meeting participants to facilitate the discussion of the meeting topics.

CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Assessment

{See appended electronic signature page}

Richard T. Lostritto, Ph.D.
Division Director
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Assessment

**Starting Materials for the Synthesis of Eribulin Mesylate
Type C Meeting – July 2, 2010**

MEETING OBJECTIVE

The objective of this meeting is to gain agreement with the FDA on the GMP starting materials for the synthesis of eribulin mesylate.

AGENDA

- 1. Introductions** (Eisai Regulatory Affairs and technical representatives) 5 minutes

Final List of Eisai Attendees (in person):

Charles Chase - Senior Scientist, Process Research
Gordon Wilkie - Senior Research Investigator, Process Research
Bryan Lewis - Senior Director, Global Project Management
Frank Fang - Vice President, US API Process Development
Katsuya Tagami - Senior Director, API Research, CMC Japan
Takashi Hasebe - Senior Scientist, Analytical Chemistry
John Orr - Director, Analytical Chemistry
Robert Costanzo - Director, Quality Control
Nicholas Tamasco - Executive Director, Global Quality Assurance
Adam Grobin - Exec. Director, Analytical Development
Michael Lewis - President, Pharmaceutical Sciences & Technology
Mark Taisey - President, Global Regulatory Affairs
Monica Lee - Director, Regulatory-CMC

- 2. Presentation** (Frank Fang) 15 minutes
- 3. Q&A Discussion** (FDA and Eisai) 40 minutes

27 Page(s) Withheld

X Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

 Law Enforcement Action (b7)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	GI-1	EISAI INC	eribulin mesylate

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

/s/

SCOTT N GOLDIE
08/27/2010

RICHARD T LOSTRITTO
09/01/2010



NDA 201532
Eisai, Inc.
Attention: Monica Lee, Director
Regulatory Affairs-CMC
300 Tice Boulevard
Woodcliff Lake, NJ 07677

INFORMATION REQUEST

Dear Ms. Lee:

Please refer to your New Drug Application (NDA) dated March 30, 2010, received March 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “Halaven (eribulin mesylate, Injection), 0.5mg/mL (1.0 mg/2 mL solution).”

We have the following comments and information requests regarding the Quality and Nonclinical sections of your submission. We request a written response by Friday, September 17, 2010, in order to continue our evaluation of your NDA.

Chemistry Manufacturing and Controls:

1. Please provide the following regarding the drug substance:
 - a. Data to support the chemical structure for each specified impurity.
 - b. Analytical results for the reference standard that address each attribute in the drug substance specification.
2. Regarding the intermediates:
 - a. Provide evidence confirming the chemical structure for key intermediates (b) (4)
[REDACTED]
 - b. Revise the acceptance criteria for total impurities in intermediates (b) (4)
[REDACTED] to more closely reflect the actual batch data.
 - c. Clarify whether the (b) (4)
[REDACTED] is used one time or multiple times. If (b) (4) is used multiple times, then provide criteria for acceptable re-use of (b) (4).

3. Regarding the revised starting materials:

- a. Revise the specification for starting material (b) (4) to include a test, method and criterion for potential enantiomer (b) (4). We note that you already monitor for this material.
- b. Specify whether you also have test methods and control strategies for potential enantiomers in starting materials (b) (4). If yes, then include the test method(s) with acceptance criteria in the specification for these two starting materials. If suitable test methods are not available, submit a plan for development of chiral specific methods, justification of the acceptance criteria, and inclusion in the specification of these (b) (4) starting materials with an appropriate timeline and mechanism of submission.
- c. Regarding the starting material (b) (4):
 - 1) Your proposed acceptance criterion for assay is (b) (4) %. This permits up to (b) (4) % impurities in the starting material. Provide data demonstrating that (b) (4) manufacturing process steps can routinely remove total impurities at this level and that impurities from this starting material are no (b) (4) into the final drug substance.
 - 2) Provide acceptance criteria with justification and test method(s) for other specified, unspecified, and total impurities. If suitable analytical method(s) and/or adequate batch data are not available to support the specification, then submit a plan to develop the method(s) and/or collect data with an appropriate timeline and mechanism for submission.
- d. Regarding the starting material (b) (4):

The August 9, 2010 amendment states that the specification listed in Table 19 was the acceptance criteria used at the time of manufacture for the lots listed in Table 21. An acceptance criterion of “for information only (FOI)” is not acceptable as a regulatory specification. Propose and justify a regulatory specification that ensures adequate quality control for starting material (b) (4). In addition, the assay criterion should be in units of weight% (not in area%).

4. Regarding the revised intermediates:

- a. For (b) (4)
 - 1) Your proposed acceptance criterion for assay is (b) (4) %. This means that other impurities (including (b) (4)) can be up to (b) (4) %. Provide data demonstrating that (b) (4) manufacturing process steps can

routinely remove impurities at this level and that these impurities will not be (b) (4) into the drug substance.

- 2) Propose acceptance criteria with justification for specified impurities (b) (4) (b) (4) "FIO" is not acceptable for a regulatory specification.
- 3) Propose acceptance criteria with justification and test method(s) for other specified, unspecified, and total impurities. If suitable test method(s) and/or adequate batch data are not available, submit a plan for development of the analytical method(s) and/or collection of data with an appropriate timeline and mechanism for submission.

b. For (b) (4)

Propose acceptance criteria with justification for specified impurities (b) (4) (b) (4) other specified, unspecified and total impurities. "FIO" is not acceptable for a regulatory specification. If suitable test method(s) and/or adequate batch data are not available, submit a plan for development of the analytical method(s) and/or collection of data with an appropriate timeline and mechanism for submission.

c. For (b) (4)

Propose a specification with justification for (b) (4). This should include, but not limited to, testing for description, identification, assay, specified impurities, unspecified impurities, and total impurities. "FOI" is not acceptable as a criterion. If suitable test method(s) and/or adequate batch data are not available, submit a plan for development of the analytical method(s) and/or collection of data with an appropriate timeline and mechanism for submission

d. For (b) (4)

- 1) Propose an acceptance criterion for appearance. "FIO" is not acceptable.
- 2) Revise the acceptance criterion for assay in unit of weight% (not in area%).
- 3) Propose acceptance criteria with justification and analytical method(s) for specified, unspecified, and total impurities. If suitable test method(s) and/or adequate batch data are not available, submit a plan for development of the method(s) and/or collection of data with an appropriate timeline and mechanism for submission.

- e. For (b) (4)
- 1) Provide an acceptance criterion for appearance. “FIO” is not acceptable.
 - 2) Propose acceptance criteria with justification for (b) (4) content.
 - 3) Propose an acceptance criterion for assay. “FIO” is not acceptable as a regulatory specification.
 - 4) Propose acceptance criteria with justification and test method(s) for specified, unspecified, and total impurities. If suitable test method(s) and/or adequate batch data are not available, submit a plan for development of the method(s) and/or collection of data with an appropriate timeline and mechanism for submission.

Nonclinical:

5. Based on the levels of impurities that were qualified by the nonclinical testing or from clinical studies using lot BRD003, adjust the acceptance criteria for the following impurities present in the drug substance and drug product to levels that do not exceed qualification values, as follows:
 - a. Drug Substance – Adjust the acceptance criteria for (b) (4) to no more than (NMT) (b) (4), and for (b) (4) to NMT (b) (4)
 - b. Drug Product – Adjust the acceptance criteria for (b) (4) to NMT (b) (4).

We are also proposing to hold a teleconference with you to provide you with an opportunity to clarify the comments in this “Information Request” letter. The teleconference is scheduled as follows:

Date: Friday, September 3, 2010
Time: 10:00 A.M. – 11:00 A.M. EST.
Phone Arrangements: Dial In Number: 866-827-9459, Passcode: 6160974

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

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

PATRICIA KEEGAN
08/30/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting
7-26-10
Memorandum

Date: August 25, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #7 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven (under review)]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Team meeting was held to discuss the CMC related issues/deadlines

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010



NDA 201532

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Eisai, Incorporated
Attention: Annmarie Petraglia
Senior Director, Global Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Petraglia:

Please refer to your new drug application (NDA) dated March 30, 2010, received March 30, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for “Halaven (Eribulin Mesylate, Injection), 0.5mg/mL (1.0 mg/2mL solution).”

On August 9, 2010, we received your August 9, 2010, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 30, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and postmarketing requirement/commitment requests by December 2, 2010.

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

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

PATRICIA KEEGAN
08/25/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

TU-VAN L LAMBERT
08/24/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: August 17, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #5 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Overall review of the Label and patient package insert with the whole review team and internal consults

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting
7-26-10
Memorandum

Date: August 10, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #6 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven (under review)]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Team meeting was held to discuss the recent submissions and the review status.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010



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

Memorandum

Date: July 30, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request regarding Study E7389-G000-301.

From: Jarral, Vaishali
Sent: Friday, July 30, 2010 10:24 AM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Information Request; NDA 201532

Ms. Petraglia,

Please submit the protocol for Study E7389-G000-301, including amendments, to NDA 201532 for clinical review. Please also include the date of the original protocol submission and the dates of any amendments that were made to the protocol.

Please submit the information above by August 4, 2010 via email and follow it with the amendment to the original NDA.

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
07/30/2010



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

Memorandum

Date: July 29, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request--Microbiology

From: Jarral, Vaishali
Sent: Thursday, July 29, 2010 11:45 AM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Information request for NDA 201532

Ms. Petrgalia,

Please see below the "information request" regarding NDA 201532. Please submit the following to me by August 6, 2010 via email followed by the formal amendment submission to the original NDA by August 10, 2010.

"For component and equipment sterilization (b) (4) please provide the following information:

- 1) (b) (4)
- 2)
- 3)
- 4)

Please confirm the receipt of this email.
Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
07/30/2010



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

Memorandum

Date: July 28, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request- Carton and Container Label.

From: Jarral, Vaishali
Sent: Wednesday, July 28, 2010 10:21 AM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Revised Carton Label- NDA 201532

Hello Ms. Petraglia,

During our review of your revised Carton and Container labeling, the Agency has noted that the carton label indicates "each vial contains 1 mg of Halaven in 2mL.." Halaven should be replaced with eribulin mesylate. Halaven is a tradename and eribulin mesylate is the API.

Please send me your revised carton label by August 2, 2010

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
07/30/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting
7-26-10
Memorandum

Date: July 26, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #5: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with metastatic breast cancer who have previously received an anthracycline, a taxane, and at least two chemotherapeutic regimens for the treatment of metastatic disease

This internal team meeting was held to discuss the internal deadlines related to this application. Other review related matters were also discussed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/07/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting
7-19-10
Memorandum

Date: July 19, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #4: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Status of the primary review and consults due dates were discussed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/07/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: July 19, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #4 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Focused on the following **Clinical Pharmacology and Clinical Studies** of the label:

**CLINICAL STUDIES
PATIENT PACKAGE INSERT
DOSE MODIFICATION**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010



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

Memorandum

Date: July 14, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request Carton and Container Label to Eisai

From: Jarral, Vaishali
Sent: Wednesday, July 14, 2010 3:13 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: NDA 201532-Labeling revisions

Ms. Petraglia,

Please see attached the list of comments from FDA regarding Carton and Container label for NDA 201532.

Please incorporate these changes to the carton and container labels and send me the mock-up of the container label and the carton labeling that shows the proposed trade dress and the recommended changes by July 20, 2010. Please provide the information requested as an amendment to the NDA as well.

Please confirm the receipt of this email.



NDA 201532
.Eribulin Carton an..

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
07/30/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: July 13, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #2 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Focused on the following **NONCLINICAL** and **CMC SECTIONS** of the label:

- 13 **NONCLINICAL TOXICOLOGY**
- 8 **USE IN SPECIFIC POPULATIONS**
- 2 **DOSAGE AND ADMINISTRATION**
- 3 **DOSAGE FORMS AND STRENGTHS**
- 11 **DESCRIPTION**
- 16 **HOW SUPPLIED / STORAGE AND HANDLING**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: July 8, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #1 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Focused on the following **CLINICAL SECTIONS** of the label:

CONTRAINDICATIONS
WARNINGS AND PRECAUTIONS
ADVERSE REACTIONS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010
Labeling Meeting #1

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: October 8, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #8 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.
Agenda: Continuation to October 5, 2010 labeling meeting to review Eisai's comments to the label and Patient package insert, corrected formatting issues, and discussed comments related to the review of the eribulin label.

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

/s/

VAISHALI JARRAL
10/12/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting Agenda
7-6-10
Memorandum

Date: July 6, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #3: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Team meeting was held to discuss the potential PMRs/PMCs of this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/07/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting
7-2-10
Memorandum

Date: July 2, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Industry Meeting: NDA 201532/0

Original Application:	NDA 201532/0
Review Status:	Priority Review
Product:	Eribulin Mesylate injection
Submission Date:	March 30, 2010
Received Date:	March 30, 2010
Sponsor:	Eisai, Incorporated
Indication:	For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Eisai, Inc requested a meeting on June 16, 2010 to discuss agency's questions or concerns about Eisai's proposed starting materials. A Type C meeting was held between ONDQA and Eisai, Inc on July 2, 2010.

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

/s/

VAISHALI JARRAL
10/12/2010

SCOTT N GOLDIE
10/13/2010

Minutes for this meeting, signed by the meeting chair, have been placed into the administrative file.



NDA 201532

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Annmarie Petraglia
Senior Director, Global Regulatory Affairs

Dear Ms. Petraglia:

Please refer to your New Drug Application (NDA) dated March 30, 2010, received March 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eribulin Mesylate for Injection, 1 mg/2 mL.

We also refer to your April 2, 2010, correspondence, received April 5, 2010, requesting review of your proposed proprietary name, Halaven. We have completed our review of the proposed proprietary name, Halaven and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your April 2, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

CAROL A HOLQUIST
07/02/2010



NDA 201532

INFORMATION REQUEST

Eisai, Inc.
Attention: Monica Lee, Director
Regulatory Affairs-CMC
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Lee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for eribulin mesylate, Injection, 0.5mg/mL (1.0 mg/2 mL solution).

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by 28 July 2010, unless otherwise specified below, in order to continue our timely evaluation of your NDA.

DRUG SUBSTANCE

1. The following comments apply to in-process control from (b) (4) of the drug substance manufacturing:
 - a) Provide justification with supporting data to demonstrate that the proposed identification test for each isolated intermediate is capable of separating the (b) (4).
In addition, for stages where a (b) (4) provide an identification test that is capable of identifying the desired stereoisomer.
 - b) Revise the acceptance criteria for total impurities of each isolated intermediate to more closely reflect the actual batch data. For example, in (b) (4) the proposed acceptance criterion for total impurities is NMT (b) (4) while actual batch data for total impurities is in the (b) (4) range.
 - c) Provide an acceptance criteria and test method for assay of each isolated intermediate. The acceptance criteria should reflect the actual batch data.
 - d) Revise the acceptance criteria for (b) (4) to more closely reflect the actual batch data. Identify the (b) (4)
2. Revise the drug substance specification to include identity and purity tests that are selective for the desired stereoisomer.

3. Revise the acceptance criteria for specified individual impurities and total impurities in the drug substance to reflect the clinical and stability batch data and current manufacturing capability.
4. Revise the linearity study for the analytical methods for (b) (4) to use a range from the limit of quantification to (b) (4) of the specification.
5. Revise the submitted historical batch analysis data for drug substance to report the actual measured value for each attribute when it is above LOQ. It is not acceptable to report “BRL”. Also, levels for (b) (4) should be reported as actual measured value (not as “each NMT (b) (4)”).

DRUG PRODUCT

1. Revise the drug product specification based the results on the batch analyses and stability study, and safety data:
 - a) Propose a test, method and acceptance criterion for (b) (4) Content. Include an appropriate validation study for the proposed analytical method.
 - b) Revise the acceptance criteria for each specified degradants/impurities (b) (4) based on safety data, batch analyses, stability data, and appropriate validation of the analytical method (detection limit and limit of quantitation).
 - c) Tighten the acceptance criterion for pH from (b) (4), based on the stability data submitted in NDA 201532.
2. Revise the validation study for the HPLC method used to determine specified and unspecified degradants/impurities to address the detection limit and quantitation limit of each of the specified and unspecified degradants/impurities per the expectations in the current USP <1225> and in the ICH Q3B(R2), Q2A and Q2B guidances. Include a statement of the reporting limit for each of the cited impurities.

STARTING MATERIALS

Based on the meeting discussion at the meeting on July 2, 2010, FDA and Eisai agree that the starting materials will be designated as compounds (b) (4)

Per the discussion, we expect the following data and information to be included in the post marketing commitment (referred to as stages 1 and 2 during the meeting). Stage 3 would be the actual submission of data and information as a post approval supplemental application as agreed to in the commitment:

STAGE 1 - Information necessary to support approvability of the application.

1. Provide in-process controls for each isolated intermediate. They should include, but are not limited to, the following:
 - a. An identification test that is capable of differentiating the (b) (4). In addition, for stages where (b) (4) provide an identification test that is selective for the desired stereoisomer.
 - b. Acceptance criteria and test methods for assay of each isolated intermediate. The proposed acceptance criteria should reflect the actual batch data.
 - c. Analytical test methods should be described in sufficient detail with representative chromatograms showing resolution of the analytes of interest.
2. Revise Section 3.2.S.2.3 Control of Materials with the same information for the revised starting materials (b) (4) as was provided for compounds (b) (4). The specification for each starting material should include identity and purity tests that are selective for the desired stereoisomer.
3. A description of stage 2 information which will be submitted.
4. A time line for the submission of the stage 2 and stage 3 information.

This information should be submitted no later than 09 August 2010.

STAGE 2 - post marketing commitment

1. Acceptance criteria and test methods for each specified impurity, unspecified impurity, and total impurities. The proposed acceptance criteria should reflect the actual batch data.
2. Provide an estimated yield for the production of each isolated intermediate.

3. Provide the results of in-process testing from the manufacturing of [REDACTED] (b) (4)
4. Characterization of the newly designated starting materials.

This information should be submitted no later than 180 days of application approval.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

RICHARD T LOSTRITTO
07/02/2010



NDA 201532

MEETING REQUEST GRANTED

Eisai Inc.
Attention: Monica Lee, Director
Regulatory Affairs-CMC
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Lee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eribulin Mesylate, Injection, 0.5mg/mL (1.0 mg/2mL solution).

We also refer to your 16 June 2010, correspondence requesting a meeting to discuss to address agency questions or concerns about your proposed starting materials. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: Friday, 2 July 2010
Time: 1100 - 1200 ET
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

Tentative CDER participants:	William M Adams	Steven Lemery
	Josephine M Jee	Richard T Lostritto
	Scott N Goldie	Anne Pilaro
	Vaishali Jarral	Ying Wang
	Lori E Kotch	Liang Zhou

Please e-mail me your attendees at scott.goldie@fda.hhs.gov, by 28 June 2010. If there are any additional foreign visitors, complete and email me the enclosed Foreign Visitor Data Request Form, as soon as possible. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have 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.

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 either of the following numbers to request an escort to the conference room: Scott N Goldie (x6-2055); the division secretary, Cathy Harrison (x6-2410).

As discussed and you agreed to, because your application is being reviewed under a **priority** review clock, we will not be able to review any new information outside what was previously submitted to the NDA prior to this meeting. You have committed to submit to the administrative file an agenda and presentation slides with references to the eCTD leaf structure in the NDA as background information for the meeting. If the materials presented in the information package are inadequate to prepare for the meeting, introduce or rely on data not currently contained in the NDA or if we do not receive your agenda and presentation by 28 June 2010, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
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 PASSPORTISSUANCE DATE:EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	Friday, 2 July 2010, 1100 ET
MEETING ENDING DATE AND TIME	Friday, 2 July 2010, 1200 ET
PURPOSE OF MEETING	Chemistry, Manufacturing and Controls Face-to-face meeting with industry
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Bldg 22 Room 1421
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Scott N. Goldie, PhD Regulatory Health Project Manager for Quality Office of New Drug Quality Assessment Center for Drug Evaluation and Research White Oak Bldg 21 Room 2553 (301) 796-2055
ESCORT INFORMATION (If different from Hosting Official)	Same as above

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	GI-1	EISAI INC	eribulin mesylate

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

/s/

SCOTT N GOLDIE
06/23/2010

Information request from Clinical Pharmacology reviewer dated June 22, 2010 with the due date of June 24, 2010.

From: Jarral, Vaishali
Sent: Tuesday, June 22, 2010 3:47 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: NDA 201532; eribulin mesylate; Eisai, Inc. Information Request

Ms. Petraglia,

Please see below the "Information request" from the Agency:

"We would like clarification from the sponsor regarding a particular analysis provided in the population PK report for the expected AUC ranges and probability of experiencing Grade 4 Neutropenia for patients with hepatic impairment. We would like the sponsor to submit the data set and the associated program codes that were used to generate Figures 28, 29 and 30 in the population PK report (Module 5.3.3.5\pooled-pop-pkpd\pooled-pop-pkpd.pdf\Sec9.4) by June 24th, 2010."

Please confirm the receipt of this email and send the response to this information request to me via email by June 24, 2010 and as an amendment to the NDA 201532.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

VAISHALI JARRAL
06/22/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Mid-Cycle Meeting
6-18-10**

Memorandum

Date: June 18, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Mid-Cycle Meeting: NDA 201532/0

Original Application: NDA 201532/0

Product: Eribulin Mesylate [Proper Name- Halaven (under review)]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

This internal mid-cycle meeting was held for the reviewers from various disciplines to internally present the application and discuss potential review issues, potential PMRs/PMCs etc.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/07/2010

**eCTD NDA 201532/0
Eribulin Mesylate
Labeling Meetings**

Memorandum

Date: July 15, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Labeling Meeting #3 NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Focused on the following **Clinical Pharmacology and Clinical Studies** of the label:

**CLINICAL STUDIES
DRUG INTERACTIONS
CLINICAL PHARMACOLOGY**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
09/13/2010

Goldie, Scott

From: Monica_Lee@Eisai.com
Sent: Wednesday, June 16, 2010 4:14 PM
To: Goldie, Scott
Subject: NDA 201532: FDA General Advice Letter dated 9 June 2010

Dear Scott:

Reference is made to Eisai's NDA 201532 and to the FDA General Advice letter dated 9 June 2010 regarding starting materials.

In this letter, the Agency requested Eisai to "revise and submit section 3.2.S.2 regarding the newly designated starting materials and relevant information....should be provided no later than 16 June 2010."

This email is to advise the Agency that we are unable to meet the 16 June 2010 target date at this time. Further discussions are ongoing internally within Eisai. I will advise you in due course.

We have not had an opportunity to meet directly with any NDA CMC chemistry reviewers to address agency questions or concerns about the proposed starting materials. We hope that even at this late stage, you will agree that the most effective way for us to clearly understand and quickly resolve this situation will be a direct dialog. Eisai continues to believe that direct dialogue with the Agency on this topic is the most efficient way to achieve mutual understanding.

Thank you for your patience.

Best regards,

Monica

Monica Lee
Regulatory Affairs-CMC
Eisai Inc.
300 Tice Boulevard
Woodcliff Lake, NJ 07677
monica_lee@eisai.com
phone: 201-949-4515

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

SCOTT N GOLDIE
06/21/2010



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

Memorandum

Date: June 11, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Filing Communication; 74 Day Letter.

From: Jarral, Vaishali
Sent: Friday, June 11, 2010 1:56 PM
To: 'Annmarie_Petraglia@Eisai.com'; 'Sheila_Talatala@Eisai.com'
Subject: NDA 201532- Filing Communication

Ms. Petraglia,

Please see attached the filing communication for NDA 201532. During the filing review of your application, the Agency identified the potential review issues and request that you address these issues by June 30, 2010, unless specified otherwise.

Please confirm the receipt of this email.



NDA201532_74DAY
S_LTR.pdf (97 K...

Thank you,
Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/19/2010



NDA 201532

FILING COMMUNICATION

Eisai, Incorporated
Attention: Annmarie Petraglia
Senior Director, Global Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Petraglia:

Please refer to your new drug application (NDA) dated March 30, 2010, received March 30, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for “Eribulin Mesylate, Injection, 0.5mg/mL (1.0 mg/2mL solution).”

During our filing review of your application, we identified the potential review issues and request that you address the following issues by June 30, 2010, unless specified otherwise:

Clinical

1. Please submit datasets and the updated survival analyses, which are or will be submitted to the EMEA, as soon as possible but no later than July 28, 2010, as a component of the 120 day safety update.
2. Please provide your rationale for inclusion of a Patient Package Insert (PPI) given that this product will be administered solely as an infusion. If, after reconsideration, you still wish to propose a PPI, please submit a revised PPI which conforms to the Medication Guide content and format requirements as set out in 21 CFR 208.20.
3. Section 10.2 of the Clinical Study Report for study E7389-G000-305 indicates that 7.7% of randomized patients failed to meet one or more of the major inclusion/exclusion criteria. The study report states that data review revealed that most of these eligibility violations were due to differing opinions of the “definition of a chemotherapy regimen than that defined in the protocol.” Please submit an explanation regarding why routine study monitoring did not detect this difference in opinion before a large number of protocol deviations occurred.
4. Please provide two alternative versions of Table 2, as currently included in Section 6.1 of the proposed physician package insert, for our review. The first alternative Table 2 should use a single column to summarize adverse events \geq Grade 3 in severity instead of using two columns to list Grade 3 and \geq Grade 4 adverse reactions. The second alternative version should provide a column of “severe” adverse reactions in addition to the total number of adverse events for each preferred term; “severe” adverse reactions

should include all adverse events of \geq grade 3 in severity by CTCAE and those that were not assigned a CTCAE grade but were considered "severe" by investigators. FDA will determine which version of the tabular summary of adverse reactions more accurately describes the adverse reaction profile of eribulin during the conduct of our review.

Clinical Pharmacology

4. Provide Appendix IV of the population pharmacokinetics (PK) report which contains the population pharmacokinetics base and final model control streams and output listings.
5. For the HPLC-ESI-MS/MS method described in report no. E7389\VAL\088:
 - a. Provide long-term stability data of eribulin in human plasma for a minimum duration of the long-term storage of the samples collected as part of studies 108, 109 and 110.
 - b. Provide methods to calculate inter-day precision and accuracy.
6. For the hepatic impairment study described in report no. E7389-E044-108:
 - a. Provide the data for the additional patient with moderate hepatic impairment enrolled into the study.

Microbiology Product Quality

7. Please submit the protocol and final study report for the microbial immersion container/closure integrity test

Pharmacology Toxicology

8. The levels of (b) (4) reported in the four most recent batches of drug substance were not reported for earlier batches, including the lots used for the toxicology studies. Provide data regarding the levels of these (b) (4) in all of the previous batches, including the toxicology lots.

Proposed Labeling

Address the following identified deficiencies/recommendations and re-submit physician product labeling in clean and red-line MS WORD versions as an amendment to your application:

9. General Comments:
 - a. Use command language throughout the label.

- b. Avoid using the words “General”, “Other”, or “Miscellaneous” for the title of a subsection (e.g. Section 2.1).
 - c. Tables and figures should not extend beyond the text margins.
 - d. Change "IV" to "intravenous infusion" throughout label.
10. Highlights Section:
- a. There should be white space between each major heading in Highlights.
 - b. Highlight Limitation Statement must be in bold type.
 - c. Include the Route of Administration immediately below the drug and drug’s dosage form.
 - d. The verbatim statement “Initial U.S. Approval” is to be followed by the four-digit year in which FDA initially approved a new molecular entity. Therefore, remove the word month from there.
 - e. If a product is a member of an established pharmacologic class, the following statement must appear under the *Indications and Usage* heading in the Highlights: “(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Please propose an established pharmacologic class that is scientifically valid and clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
 - f. A concise summary of Dosage forms and Strengths should include an appropriate subheading (e.g. tablets, capsules, injectable, suspension).
 - g. You must reference Pregnancy subsection (8.1) in third bullet under *Warning and Precautions*.
 - h. The full prescribing information (FPI) contains a section - *Use in Specific Populations*. Corresponding section and subsection must be listed in the highlights section.
 - i. The Patient Counseling Information statement (must appear in bold type) and “Patient Counseling Information” should be in upper-case letters.
 - j. Regarding the revision date, the preferred format is - Revised: Month/Year (the colon is missing in your proposed label).
 - k. A horizontal line must separate the Highlights, Contents, and FPI.
11. Full Prescribing Information - Contents (Table of Contents):

- a. Avoid using acronyms in subsection headings. Please refer to the Institute for Safe Medication Practices (ISMP's) website (<http://www.ismp.org/Tools/abbreviationslist.pdf>) for list of error-prone abbreviations, symbols, and dose designations.
 - b. Remove Section 17.3 from the content and the FPI. Please refer to 12(e) for more details.
12. Full Prescribing Information (FPI):
- a. The preferred presentation of cross-references in the FPI is the section heading followed by the numerical identifier. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print as was done in Section 5.1, 2nd line.
 - b. Please remove the bullet from the sentence before section 6.1.
 - c. Under *Pharmacokinetics* (section 12.3), do not number headings within a subsection (e.g. 12.3.1). Use headings within a subsection without numbering.
 - d. Since subsection 12.4 is a specific subsection restricted to *Microbiology* and 12.5 restricted to *Pharmacogenomics*, do not use these subsection numbers for other subsection headings. If warranted, subsection 12.6 can be created for other Clinical Pharmacology topics that do not fall within the subsection headings 12.1 thru 12.5. When a specified subsection is omitted, the numbering does not change.
 - e. The *Patient Counseling Information* (section 17) must reference any FDA-approved patient labeling or Medication Guide. The reference [See FDA Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence. Remove Section 17.3.

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.

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

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

PATRICIA KEEGAN
06/10/2010



NDA 201532

GENERAL ADVICE

Eisai Inc.
Attention: Monica Lee, Director
Regulatory Affairs-CMC
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Lee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eribulin Mesylate, Injection, 0.5mg/mL (1.0 mg/2mL solution).

We also refer to your email correspondence of 26 May 2010 in response to our information request letter dated 13 May 2010, containing a request for a dialog to elaborate on the Agency's comments on your proposed starting materials for synthesis of your drug substance.

We have reviewed the referenced material and have the following comments.

1. We refer to the minutes of the End of Phase 2 meeting held on 14 April 2006 for IND 67193 which reflects discussions regarding your starting materials. FDA rejected your proposed starting materials: compounds (b) (4). FDA stated that further discussion regarding the starting materials would be considered if "substantial additional information pertaining to the proposed starting materials" were submitted. After reviewing the information submitted in the NDA, we have concluded that your proposed starting materials, compounds (b) (4), are not acceptable. We stated this in our letter dated May 13, 2010. We reiterate our recommendations from that letter that the appropriate starting materials are compounds (b) (4). Key intermediates ((b) (4)) need to have good manufacturing quality control and need to be manufactured under cGMP. Therefore, starting materials should be manufactured (b) (4).
2. We refer to the agency correspondence of 27 May 2010 notifying you of the determination that the review classification of your application is a **priority** review. In order for us to continue our review of the Quality section (eCTD Module 3), you need to revise and submit section 3.2.S.2 regarding the newly designated starting materials and relevant information requested in our 13 May 2010 letter. The information should be provided no later than 16 June 2010. Under the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*, we have established internal review timelines as well as the expectation that information requested by the Agency will be provided in a timely fashion in order to maximize the efficiency of the review process. As such, we do not find it necessary to hold additional negotiations regarding your starting materials at this time.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

WILLIAM M ADAMS

06/09/2010

William Adams. acting for Sarah Pope Miksinski

Information Request from Clinical, dated 6/4/10

From: Jarral, Vaishali
Sent: Friday, June 04, 2010 2:06 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Information Request; NDA 201532- Datasets

Hello Ms. Petraglia,

Please see the following information request:

1. Please provide the location in the datasets that provides protocol deviation data.
2. Please provide the location in the datasets that provides information regarding the number of patients who have locally advanced disease versus metastatic disease. We are unable to make an educated guess regarding the minimum number of patients enrolled with metastatic disease based upon the locations of disease involvement in the dataset, but it isn't clear how to find the exact number of patients who were enrolled with locally advanced disease.

Please send the information requested above to me via email by Thursday June 10, 2010. Also, provide this information via amendment to the NDA.

Please confirm the receipt of this email. Thank you,

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

VAISHALI JARRAL
06/22/2010

eCTD NDA 201532/0
Eribulin Mesylate
First Team Meeting
6-1-10
Memorandum

Date: June 1, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #2 : NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven (under review)]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

The agenda for Mid-Cycle, labeling meetings and other review related internal dates were discussed

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/07/2010



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

Memorandum

Date: May 28, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Priority Review Determination Notification

Ms. Petraglia,

Please see attached the "Priority Review Determination" letter for NDA 201532. This letter will be delivered to you via post as well.

Please confirm the receipt of this email.

Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248



NDA_201532_Priorit
y Review Determinati

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/19/2010



NDA 201532

PRIORITY REVIEW DESIGNATION

Eisai, Incorporated
Attention: Annmarie Petraglia
Senior Director, Global Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Petraglia:

Please refer to your new drug application (NDA) dated March 30, 2010, received March 30, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for "Eribulin Mesylate, Injection, 0.5mg/mL (1.0 mg/2mL solution)."

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is September 30, 2010

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 commitment requests or postmarketing requirements by September 2, 2010.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before June 11, 2010.

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

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
05/26/2010

PATRICIA KEEGAN
05/27/2010

Goldie, Scott

From: Monica_Lee@Eisai.com
Sent: Wednesday, May 26, 2010 2:45 PM
To: Goldie, Scott
Subject: NDA 201532: Questions and Request for Meeting Regarding Starting Materials
Importance: High

Dear Scott:

Reference is made to our May 20, 2010 phone conversation during which you informed me that it is not the policy of ONDQA to grant ad hoc meetings to a sponsor without first receiving written questions from the sponsor.

Accordingly, Eisai hereby submits the following questions and a request for a face-to-face meeting between Eisai representatives and the FDA chemistry review team. Please let me know if I can be of further assistance to you.

Reference is made to the FDA's letter dated May 13, 2010 pertaining to Eisai's NDA 201532 for Eribulin Mesylate Injection. The letter contained the Agency's comments on our proposed starting materials of synthesis and drug product specifications.

Thank you for your letter of May 13, 2010 in which you expressed concerns about "control of potential by-products from (b) (4) (b) (4)," and concluded that (b) (4) are appropriate starting materials. Eisai appreciates the Agency's recommendation. We had in the past also considered designating these compounds as starting materials. However, during the pharmaceutical development program, controls following (b) (4) were established that effectively control finished drug substance quality.

We would appreciate an opportunity to more fully explain these controls and why we believe (b) (4) are the most appropriate starting materials. With that in mind we have formulated the following specific questions for consideration and discussion:

1. Regarding "control of potential by-products from (b) (4)," with the Agency's recommendation of (b) (4), does the agency have specific concerns about stereochemical quality control at (b) (4) ?
2. Regarding "control of potential by-products from (b) (4)," with the Agency's recommendation of (b) (4), does the agency have specific concerns about stereochemical quality control at (b) (4) ?
3. Would the Agency be willing to open a dialog with us to elaborate further on their concerns over (b) (4) being the regulatory GMP starting materials?

Eisai requests the opportunity to meet with the CMC review team to more fully explain the stereochemical quality control points for (b) (4), and other potential impurities for which you may have concern. We suggest that the format of this meeting will include a set of very concise slides prepared by Eisai illustrating such control points.

Eisai would like to request that this face-to-face meeting take place the week of June 14, 2010.

Best regards,

Monica

Monica Lee
Regulatory Affairs-CMC
Eisai Inc.
300 Tice Boulevard
Woodcliff Lake, NJ 07677
monica_lee@eisai.com

6/9/2010

phone: 201-949-4515

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.]

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	GI-1	EISAI INC	eribulin mesylate

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

/s/

SCOTT N GOLDIE
06/09/2010



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

Memorandum

Date: May 25, 2010

From: Vaishali Jarral, Regulatory Project Manager

Subject: *NDA 201532*

Phone conversation between CDTL (Dr. Steven Lemery) and Eisai, Inc.

Eisai, Inc (Contact person: Annmarie Petraglia) was notified that FDA has decided not to take NDA 201532 (eribulin mesylate) to the advisory committee. Applicant acknowledged, and no further question was asked by the applicant.

Call concluded.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
05/25/2010



NDA 201532

INFORMATION REQUEST

Eisai Inc.
Attention: Monica Lee
Regulatory Affairs-CMC
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Lee:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eribulin Mesylate, Injection, 0.5mg/mL (1.0 mg/2mL solution).

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by 26 May 2010, in order to continue our evaluation of your NDA.

1. We have reviewed the proposed synthesis scheme for the manufacture of starting materials and of finished drug substance and have taken into account the discussions at the end of phase 2 meeting held on 14 Apr 2006. Our conclusion is that the appropriate starting materials for the proposed drug substance synthesis process are compounds (b) (4). These compounds were selected for

(b) (4)

We define (b) (4) designated starting materials to be the compounds obtained by the synthesis process described in the NDA (including the raw material specifications, process parameters and process controls) which provides for a known qualitative and quantitative impurity profile, and justifies the proposed acceptance specification.

Revise NDA section 3.2.S.2 to redefine the starting materials; to define the qualitative and quantitative impurity profiles for these materials; and to provide acceptance specifications for these materials. The acceptance specification should include an identity test which is selective for the specific (b) (4). Justification for the proposed acceptance criteria should be based on the capability of the follow-up manufacturing steps to eliminate the impurities present in the starting materials and/or the (b) (4) which they form.

In addition, provide the complete address (street, city, country and area code) and contact information (on site contact person, e-mail address, facsimile and voice telephone numbers) for the sites where these compounds are manufactured.

2. Revise the drug product specification to include a single set of criteria for product release and for use in the stability studies.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

WILLIAM M ADAMS

05/13/2010

William Adams acting for Sarah Pope Miksinski

eCTD NDA 201532/0
Eribulin Mesylate
First Team Meeting
5-11-10
Memorandum

Date: May 11, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Team Meeting #1 : NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven (under review)]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

This internal team meeting was held to discuss the application among reviewers.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
08/07/2010



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

Memorandum

Date: May 5, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Teleconference with Eisai, Inc; ODAC meeting notification

FDA Representatives:

Steven Lemery, Clinical reviewer, Team Leader (CDTL)
Vaishali Jarral, Regulatory Project Manger

Eisai, Inc. Representatives:

Corina Akerele, M.D., Director, Oncology
Paul A. Andrews, Ph.D., Executive Director, Global Regulatory Affairs - Nonclinical
Alton B. Kremer, M.D., Senior Vice President, Clinical Development, Oncology
Annmarie Petraglia, M.S., M.B.A., Senior Director, Global Regulatory Affairs - Oncology
Larisa Reyderman, Ph.D., Director, Clinical Pharmacology
Mark Taisey, BSc., President, Global Regulatory Affairs
Sheila Talatala, Pharm.D., Manager, Regulatory Affairs - Oncology
Jon Wong, Ph.D., Vice President, Global Regulatory Affairs - Oncology
Xiaosha Zhang, Ph.D., Senior Director, Biostatistics – Oncology

Meeting minutes:

Purpose: FDA requested this teleconference to notify Eisai Inc about ODAC meeting.
Discussion during the meeting:

FDA notified Eisai, Inc the following:

- There will be an ODAC meeting for NDA 201532, with tentative dates of September 1 or 2, 2010
- Reminded company that the Sept 2010 ODAC is NOT public at this time & information regarding this matter should not be disclosed until the FR publishes.
- Nicole Vesely will follow-up with a letter informing Eisai, Inc of their deadlines.

Call Concluded

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
05/06/2010



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

Memorandum

Date: May 5, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request ECG Waveforms (From IRT-QT consult).

From: Jarral, Vaishali
Sent: Wednesday, May 05, 2010 12:03 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Information Request- NDA 201532- ECG Waveforms

Ms. Petraglia,

The Agency needs the following in order to conduct a review for NDA 201532:

- Please submit all ECG waveforms, related to QT Study Report E7389-E044-110, to the ECG warehouse at www.ercgwarehouse.com.

Provide the information to me by May 12, 2010. Please confirm the receipt of this email.

Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
05/06/2010



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

Memorandum

Date: May 4, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532/0*
Information Request concerning BIMO inspections to Eisai, Inc.

From: Jarral, Vaishali
Sent: Tuesday, May 04, 2010 5:07 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Information Request; NDA 210532- Potential BIMO inspections

Ms. Petraglia,

The Agency has the following requests for information regarding potential Bioresearch Monitoring (BIMO) inspections associated with the pivotal study in support of NDA 201532.

- The copies of the contract between (b) (4) and Eisai, Inc related to the study 305. According to the Transfer of Obligations that was provided in NDA 201532 Module 1 (b) (4) is responsible for monitoring clinical investigators, obtaining information from clinical investigators and providing clinical investigators with information needed to conduct the investigation properly.
- The Agency needs the Location where Eisai, Inc stores all study [305] related documents. We need the name of authorized person of contact, address and phone number
- In addition, please provide us with the location of the (b) (4) office that has remaining records for study 305. We also need name of authorized person of contact, address and phone number associated with that location.

Please SUBMIT the information requested above to the NDA 201532. We need the information above by COB Thursday May 6, 2010.

Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

VAISHALI JARRAL
05/06/2010



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

Memorandum

Date: May 4, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532*
Email communication with Eisai, Inc.

From: Jarral, Vaishali
Sent: Tuesday, May 04, 2010 5:07 PM
To: 'Annmarie_Petraglia@Eisai.com'
Subject: Information Request; NDA 210532- Potential BIMO inspections

Ms. Petraglia,

The Agency has the following requests for information regarding potential Bioresearch Monitoring (BIMO) inspections associated with the pivotal study in support of NDA 201532.

- The copies of the contract between (b) (4) and Eisai, Inc related to the study 305. According to the Transfer of Obligations that was provided in NDA 201532 Module 1, (b) (4) is responsible for monitoring clinical investigators, obtaining information from clinical investigators and providing clinical investigators with information needed to conduct the investigation properly.
- The Agency needs the Location where Eisai, Inc stores all study [305] related documents. We need the name of authorized person of contact, address and phone number
- In addition, please provide us with the location of the (b) (4) office that has remaining records for study 305. We also need name of authorized person of contact, address and phone number associated with that location.

Please SUBMIT the information requested above to the NDA 201532. We need the information above by COB Thursday May 6, 2010.

Thank you,

Vaishali Jarral, M.S., M.B.A.
Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
CDER/FDA
301-796-4248

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
05/04/2010

eCTD NDA 201532/0
Eribulin Mesylate
Filing Meeting
5-03-10
Memorandum

Date: May 3, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Filing Meeting: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven (under review)]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

This Internal filing meeting was held to discuss the fileability of this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
05/06/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Devi Kozeli OND/ODE1/DCRP**

FROM (Name, Office/Division, and Phone Number of Requestor): **Vaishali Jarral/OODP/DBOP-301-796-4240**

DATE
4.29.10

IND NO.

NDA NO.
201532

TYPE OF DOCUMENT
Original
Application

DATE OF DOCUMENT
3/30/10

NAME OF DRUG
Eribulin Mesylate

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Small Molecule

DESIRED COMPLETION DATE
June 1, 2010

NAME OF FIRM: **Eisai, inc**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: **Request for review of QT protocol/study report for NDA 201532**

SIGNATURE OF REQUESTOR
Vaishali Jarral

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
04/29/2010



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

Memorandum

Date: April 29, 2010
From: Vaishali Jarral, Regulatory Project Manager
Subject: *NDA 201532*
Phone and email conversation between DSI and Eisai, Inc.

From: Iacono-Connor, Lauren
Sent: Thursday, April 29, 2010 3:03 PM
To: Sheila_Talatala@Eisai.com; Annmarie_Petraglia@Eisai.com
Cc: Iacono-Connor, Lauren; Jarral, Vaishali; Donoghue, Martha; Lemery, Steven
Subject: RE: Eribulin NDA 201532 - Phone conversation
Importance: High

Annmarie and Sheila,

I have a couple of requests for information related to Bioresearch Monitoring (BIMO) inspection planning in support of NDA 201532.

First, I need copies of the Charter and Contract for (b) (4), related to study 305. Based on the Transfer of Obligations declaration provided in your NDA 201532 Module 1, for study 305 (b) (4) was responsible for Monitoring Clinical Investigators, Obtaining information from Clinical Investigators and Providing Clinical Investigators with information needed to conduct the investigation properly. If these documents are already in the NDA please point me to them. If they are not, I ask that you submit them to the NDA 201532 as soon as possible.

Second, I need the geographic location where Eisai Inc stores all study [305] related documents. We plan to conduct a BIMO sponsor inspection in support of the NDA review. I am assuming that this is your location in New Jersey and if yes, would then conduct the inspection at that location. Please confirm as soon as possible.

Please contact me at your earliest convenience if you have questions.

Thank you,

Lauren

*Lauren Iacono-Connors, Ph.D.
Good Clinical Practices Branch 2
Division of Scientific Investigations, Bldg 51
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993*

301-796-3383 (office)

301-847-8748 (fax)

Lauren.IaconoConnors@fda.hhs.gov

From: Sheila_Talatala@Eisai.com [mailto:Sheila_Talatala@Eisai.com]

Sent: Wednesday, April 28, 2010 4:03 PM

To: Iacono-Connor, Lauren

Cc: Annmarie_Petraglia@Eisai.com

Subject: Eribulin NDA 201532 - Phone conversation

Dear Dr. Iacono-Connors,

Thank you for your call today. As discussed, I will inform Annmarie of your call regarding the sponsor and site inspections, and will ask her to follow-up with you by next Monday. In the meantime, if you are in need of any additional information, please let me know.

Regards,

Sheila

Sheila Talatala, Pharm.D.

Manager, Regulatory Affairs - Oncology

Eisai, Inc.

300 Tice Boulevard

Woodcliff Lake, NJ 07677

Tel: 201.949.4738

Fax: 201.949.4915

Email: sheila_talatala@eisai.com

[This e-mail message may contain privileged, confidential and/or proprietary information of Eisai. If you believe that it has been sent to you in error, please contact the sender immediately and delete the message including any attachments, without copying, using, or distributing any of the information contained therein. This e-mail message should not be interpreted to include a digital or electronic signature that can be used to authenticate an agreement, contract or other legal document, nor to reflect an intention to be bound to any legally-binding agreement or contract.].

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
04/29/2010

eCTD NDA 201532/0
Eribulin Mesylate
Team Meeting Agenda
4-26-10
Memorandum

Date: April 26, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: Applicant Orientation Presentation: NDA 201532/0

Original Application: NDA 201532/0
Review Status: Priority Review
Product: Eribulin Mesylate injection [Proper Name- Halaven]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

Agenda: Applicant Orientation meeting was held on April 26, 2010 at the White Oak campus. During this meeting, Eisai, Inc gave an overview of the application (NDA 201532).

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

/s/

VAISHALI JARRAL
10/12/2010



NDA 201532

GENERAL ADVICE

Eisai Inc.
Attention: Annemarie Petraglia
Senior Director, Global Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Petraglia:

On April 13, 2010, this office inadvertently copied a third party on an internal FDA email message regarding your NDA. This email message only contained the drug name, NDA number, and reference to "new molecular entity."

In a telephone conversation on April 13, 2010, the third party recipient of the email message agreed to delete the message. On the same day, the third party individual confirmed by email that the unintended message had been deleted.

I apologize for this inadvertent disclosure of your information. Please note that we take our disclosure responsibilities very seriously and take every effort to ensure that information is disclosed only in accordance with applicable laws and regulations.

If you have any questions, call Deborah Mesmer, Regulatory Project Manager for Quality, at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Michael Folkendt, M.S.
Associate Director Regulatory Affairs
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate

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

/s/

MICHAEL M FOLKENDT
04/26/2010

eCTD NDA 201532/0
Eribulin Mesylate
First Committee Meeting
4-15-10

Memorandum

Date: April 15, 2010

From: Vaishali Jarral, DBOP/OODP/CDER

Subject: First Committee Meeting: NDA 201532/0

Original Application: NDA 201532/0

Product: Eribulin Mesylate [Proper Name- Halaven (under review)]
Submission Date: March 30, 2010
Received Date: March 30, 2010
Sponsor: Eisai, Incorporated
Indication: For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

This internal committee meeting was held to discuss the timelines for this application including the dates for labeling meetings, mid-cycle, team meetings etc. The reviewers from various discipline were introduced to each other. The need for various consults was determined.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
04/29/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **CDER PMHS**
cc: **Rosemary Addy**

FROM (Name, Office/Division, and Phone Number of Requestor): **Vaishali Jarral/RPM/DBOP, 301-796-4248**

DATE
4/14/10

IND NO.

NDA NO.
201532

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
March 30, 2010

NAME OF DRUG
Eribulin Mesylate

PRIORITY CONSIDERATION
Priority Review

CLASSIFICATION OF DRUG
Small Molecule

DESIRED COMPLETION DATE
"ongoing"

NAME OF FIRM: **Eisai, inc**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: PMHS review of labeling submitted in Original NDA 201532 is requested to provide review and revisions to appropriate sections. Labeling meeting invitations will be sent to the assigned PMHS reviewer. The Sponsor's proposed labeling can be found in the EDR under NDA 201532 as an eCTD submission or in DARRTS.

The action goal date for the supplement is 09/30/2010.

SIGNATURE OF REQUESTOR
Vaishali Jarral, RPM

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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

/s/

VAISHALI JARRAL
04/14/2010



NDA 201532

NDA ACKNOWLEDGMENT

Eisai, Incorporated
Attention: Annmarie Petraglia
Senior Director, Global Regulatory Affairs
300 Tice Boulevard
Woodcliff Lake, NJ 07677

Dear Ms. Petraglia:

We have received your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Eribulin Mesylate, Injection, 0.5mg/mL (1.0 mg/2mL solution)

Date of Application: March 30, 2010

Date of Receipt: March 30, 2010

Our Reference Number: NDA 201532

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 May 28, 2010 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.

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 Biologics Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

If you have any questions, please call me at (301) 796-4248.

Sincerely,

{See appended electronic signature page}

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

Enclosure: GRMP Checklist and Instructions

Quality Assessment for NDA/BLA Submissions

Purpose: This assessment is intended to be used by both the applicant and members of CDER's review team. It is designed to guide them through the pertinent sections of an application and to assist in assessing the content of the NDA/BLA submission as well as the overall review process. It is to be used to record information solely to facilitate discussion of lessons learned at the post-action feedback meeting of both parties. It is to play no role in the FDA action taken on an application and is not to be used in dispute resolution. It will not be archived with the application by FDA.

When to Use: At this time, CDER will offer this assessment and the post-action feedback meeting for all NMEs and original BLAs; CDER may offer these for other applications and supplements. The Quality Assessment form should be distributed to each of the review team members, as well as to the applicant, at the pre-NDA/BLA meeting with an explanation of how it will be used. If a pre-NDA/BLA meeting is not held, this assessment should be provided to the applicant via email. Both the applicant and review team members are encouraged to periodically add information to their Quality Assessment form during the review process. This assessment should be used to guide post-action feedback meetings between the FDA and the application.

Instructions for Completing the Quality Assessment

FDA: This assessment is to be filled out during the review cycle by individual reviewers as issues relating to the review and application arise. It should be completed by the end of the review and used during the post-action feedback meetings with the applicant. Reviewers should capture as much additional information as possible on the last page of the assessment.

Applicant: This assessment should be filled out both while preparing the submission and during the review cycle. You can use it to record your experience with the review process, including the steps preceding submission of the BLA/NDA.

The Post-Action Feedback Meeting: This assessment will be used in the post-action feedback meeting only as a guide for the discussion. The applicant and all CDER reviewers should bring their completed assessment and use it as a reference for issues that are pertinent to the discussion. Due to the sizable content of the assessment, it is not expected that every question be discussed. The meeting should focus on those items that provide lessons learned (i.e., things that worked well and things that did not) for future applications.

Collection and Archiving: This assessment is not to be collected and it is not to be archived. It is for the applicant and each CDER reviewer to retain and dispose of at their discretion.

Quality Assessment for NDA/BLA Submissions

Applicant Assessment Applicant: _____
 FDA Assessment OND Division: _____

NDA# _____ BLA# _____
 Action on Application: _____ (after ____ review cycles)
 Number of amendments: _____ (including ____ major amendments)

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
Pre- and Peri-Submission Activities	A Target Product Profile (TPP) was used during drug development that improved the review process by aligning sponsor goals with proposed label claims during the IND process. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf	
	Special Protocol Assessments were utilized and benefited the application.	
	The pre-NDA/BLA meeting included discussion of all topics important for preparation of a complete, high quality application.	
	(If electronic submission) A pre-NDA/BLA application format discussion, held with FDA in advance of submission, facilitated development of a higher quality application.	
	The FDA indicated prior to submission that test results appeared to meet pre-specified endpoints and should be submitted for review.	
	An (optional) orientation session was held (within 21 days of submission) to permit applicant to familiarize reviewers with the content and navigation of the submission; this resulted in a more efficient FDA review.	
	Leading up to submission, interactions between FDA and the applicant throughout the drug development process were optimal for developing a high quality application.	
Overall Application Format and Content	The presentation and construction of the application followed the required format and was indexed appropriately.	
	(If electronic submission) The electronic submission loaded without difficulty.	

Quality Assessment for NDA/BLA Submissions

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	(If electronic submission) Proper eCTD lifecycle XML relationships were established in all submissions.	
	(If electronic submission) All hyperlinks in the application worked appropriately.	
	The application included: <ul style="list-style-type: none"> • Required forms appropriately completed • Information requested by FDA during pre-submission drug development and per applicable guidance and regulations 	
	The application appropriately reflected previous advice and requests from FDA (e.g., regarding development program, study design and endpoints, GCP issues and analysis of results, CMC issues) or included reasonable justification for all deviations from FDA guidance or pre-submission advice.	
Summaries/ Overviews	The summaries highlighted the important issues.	
	The summaries accurately reflected supporting data, including appropriate links.	
Technical Sections	Datasets were complete and in a format to facilitate FDA analysis.	
	Appropriate analyses were performed by the applicant to evaluate efficacy, safety, and product quality, e.g., claims were based on pre-specified endpoints and analyses; any deviations justified; conformed to ICH and other guidelines.	
Site Inspections	Facilities were available for inspection upon application submission.	
	Facility inspections were completed in a timely manner.	
	Clinical site inspections were completed in a timely manner.	

Quality Assessment for NDA/BLA Submissions

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	All deviations from GCP were identified for each clinical site in the initial submission and impact of deviations were discussed in the application.	
Post-marketing Requirements (PMR) and Commitments (PMC)	PMRs and PMCs, with timelines, conforming to ICH guidelines were included in the initial submission. Examples include PREA studies, confirmatory studies for accelerated approval, studies to evaluate previously identified safety issues.	
	If the need for PMRs or PMCs was identified by FDA during application review, discussion of postmarketing study proposals and timelines followed GRMP timelines.	
Risk Evaluation and Mitigation Strategy (REMS)	REMS, as discussed during pre-submission meeting, were included in the initial submission.	
	If a need for REMS was identified by FDA during application review, request for/discussion of REMS followed GRMP timelines.	
	FDA provided rationale for modifications to applicant's REMS.	
	Applicant followed FDA Guidance regarding content/organization of REMS.	
Labeling	Labeling contained annotations and/or hyperlinks to the location of supporting data in the application.	
	All references in proposed labeling were included in the submission.	
	Applicant followed FDA Guidance regarding content/organization of labeling, including patient labeling or Medication Guide and carton/container labeling.	
	FDA provided rationale for substantive modifications to applicant's labeling and FDA proposed changes were consistent with Guidances/policy.	
	FDA and applicant followed GRMP timelines for labeling discussions.	

Quality Assessment for NDA/BLA Submissions

Review Phase	Activity	Provide comments or specific examples to characterize application quality and facilitate discussion (e.g., if you don't think communication was timely, describe the frequency versus your expectation).
	Applicant's submission of proprietary name review request followed FDA guidance (e.g., more than on proposed name). If submitted during the IND review, did this "add value" to proprietary name review? If not, why not?	
Communi- cation	FDA requests for information were clearly stated and reflected understanding of application contents.	
	The applicant responded to information requests raised during the review in a <i>timely</i> manner, including: <ul style="list-style-type: none"> • Information requests during first 60 days • Day-74 letter • Information requests after 60 days • Discipline Review letters 	
	Applicant responded to issues raised during the review in a <i>complete</i> manner, i.e., no follow-up was required.	
	Did application contain information requested during IND review? Were there deficiencies communicated by FDA during the review (e.g., day 74, etc.) that should have been anticipated based on FDA comments prior to submission of the application?	
	Could issues raised by FDA during application review have been identified by FDA or applicant prior to submission?	
	How might communication or discussion of information requests been more efficient?	
	Significant deviations from the milestone timeline by FDA were communicated to the applicant.	

Quality Assessment for NDA/BLA Submissions

Additional comments from any disciplines or consultant reviewers:

Overall Assessment:

- Identify three critical factors that contributed to the application's outcome.
 - 1.
 - 2.
 - 3.
- In retrospect, would a refusal-to-file decision have better utilized resources and expedited time to approval?

- Provide any comments on how to improve the process.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate.

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

/s/

VAISHALI JARRAL
04/12/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-201532	----- ORIG-1	----- EISAI INC	----- eribulin mesylate.

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

/s/

VAISHALI JARRAL
04/07/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **CDER/SEALD**
Study Endpoints and Labeling
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411
SEALD.ENDPOINTS@FDA.HHS.GOV

FROM (Name, Office/Division, and Phone Number of Requestor): **Vaishali**
Jarral RPM/DBOP; 301-796-4248
DBOP/ODDP/OND/CDER/FDA

DATE
April 6, 2010

IND NO.

NDA NO.
201532/0

TYPE OF DOCUMENT
NME/ Original NDA

DATE OF DOCUMENT
3/30/10

NAME OF DRUG
Eribulin Mesylate (Injection)

PRIORITY CONSIDERATION
Priority Review (6
months)

CLASSIFICATION OF DRUG
Oncology (Small
Molecule)

DESIRED COMPLETION DATE
07/01/10

NAME OF FIRM: **Eisai, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: DBOP is requesting SEALD review for the label submitted in the original NDA 201532/0 to get advice regarding labeling language. Labeling meeting invitations will be sent to the assigned OSE reviewer. The Sponsor's proposed labeling can be found in the EDR under STN 201532/0 as an eCTD submission. The action goal date for this original application is 09/30/10; consult review of this application is requested by 07/01/10.

SIGNATURE OF REQUESTOR
Vaishali Jarral, RPM

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate.

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

/s/

VAISHALI JARRAL
04/07/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Vaishali Jarral RPM/DBOP; 301-796-4248 DBOP/OODP/OND/CDER/FDA
------------------------------	---

REQUEST DATE April 7, 2010	IND NO.	NDA/BLA NO. 201532/0	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) NME/ Original NDA, Submitted and Received 3/30/10
--------------------------------------	---------	--------------------------------	---

NAME OF DRUG Eribulin Mesylate (Injection)	PRIORITY CONSIDERATION Priority Review (6 months)	CLASSIFICATION OF DRUG Oncology (Small Molecule)	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 07/15/10
--	---	--	---

NAME OF FIRM: Eisai, Inc.	PDUFA Date: September 30, 2010
-------------------------------------	---------------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
---	--	--

EDR link to submission: <\\cdsesub1\evsprod\NDA201532\201532.enx>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: Close to June 30, 2010

Labeling Meetings: [None planned yet]

Wrap-Up Meeting: End of August or first week of September, 2010

SIGNATURE OF REQUESTER
Vaishali Jarral

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

	<input checked="" type="checkbox"/> eMAIL	<input type="checkbox"/> HAND

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate.

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

/s/

VAISHALI JARRAL

04/08/2010

This is the revised DDMAC Consult.

REQUEST FOR CONSULTATION

TO (Office/Division): David Hussong/Jim McVey/Sylvia Gantt
NEW DRUG MICROBIOLOGY STAFF
OC/OO/CDER/OPS/NDMS - HFD-805

FROM (Name, Office/Division, and Phone Number of Requestor): Liang Zhou
through Debbie Mesmer, Office of New Drug Quality
Assessment, 301 796-4023

DATE
April 8, 2010

IND NO.

NDA NO.
201532

TYPE OF DOCUMENT
NDA original submission

DATE OF DOCUMENT
received March 30, 2010

NAME OF DRUG
eribulin mesylate Injection

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Oncology

DESIRED COMPLETION DATE
June 30, 2010

NAME OF FIRM: Eisai Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: ONDQA/OODP is requesting to have a microbiology review of Eisai Inc.'s NDA 201532 for eribulin mesylate injection for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

This is a priority review. Please notify Debbie Mesmer of the assigned reviewer.

Link to submission: \\cdsesub1\evsprod\NDA201532\201532.enx

Ying Wang is the primary CMC reviewer.

Liang Zhou is the chemistry Team Lead (PAL)

Vaishali Jarral is the OND RPM

Debbie Mesmer is the ONDQA RPM

SIGNATURE OF REQUESTOR { See appended electronic signature page }	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate.

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

/s/

DEBORAH M MESMER
04/08/2010

LIANG ZHOU
04/08/2010