CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201532

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Division of Biologic Oncology Products
Tel. 301.796.2320

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: NDA 201532

Name of Drug: Halaven (eribulin mesylate) Injection

Sponsor: Eisai, Incorporated

Material Reviewed: Carton and Container Labels

Submit Date: March 30, 2010

Receipt Date: March 30, 2010

On March 30, 2010, Eisai, Incorporated submitted an original New Drug Application for eribulin mesylate (STN 201532/0) indicated 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.

Halaven is a clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol:water. The concentrate is supplied as 1mg/2mL in a single use vial. Halaven will be packaged as one vial per carton.

The Office of New Drug Quality Assessment (ONDQA) and the Division of Medication Error Prevention and Analysis (DMEPA) reviewed Eisai's proposed Halaven carton and container labels and package insert label.

During a labeling meeting held on July 13, 2010, DBOP received the collective DMEPA and ONDQA container label and carton labeling recommendations and a consensus on recommended changes was reached during the labeling meeting. These recommendations were forwarded to Eisai on July 14, 2010.

The following FDA labeling comments were conveyed to Eisai, Inc on July 14, 2010 via email:

(b) (4)

Carton Label:

1. Change “Tradename” to Halaven
2. The established name should be “(eribulin mesylate) injection”.
3. Revise the statement of strength to read:

   1 mg/2 mL
   (0.5 mg/mL)
4. Relocate the statement of strength to the line below the established name.
5. On the back panel, list the inactive ingredients.
6. On the back panel, relocate the storage statement to a less prominent location at the lower portion of the back panel.
7. The route of administration statement is not present. Place the route of administration statement, “For intravenous use”, below the strength.
8. Add “Sterile Solution” on the front panel.
9. Add the statement “Single use vial—discard unused portion”
10. Revise the storage statement to “Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F). Do not freeze or refrigerate.”
11. Add the statement, “Caution: Cytotoxic Agent” to the front and back panel of carton label.

(b) (4)

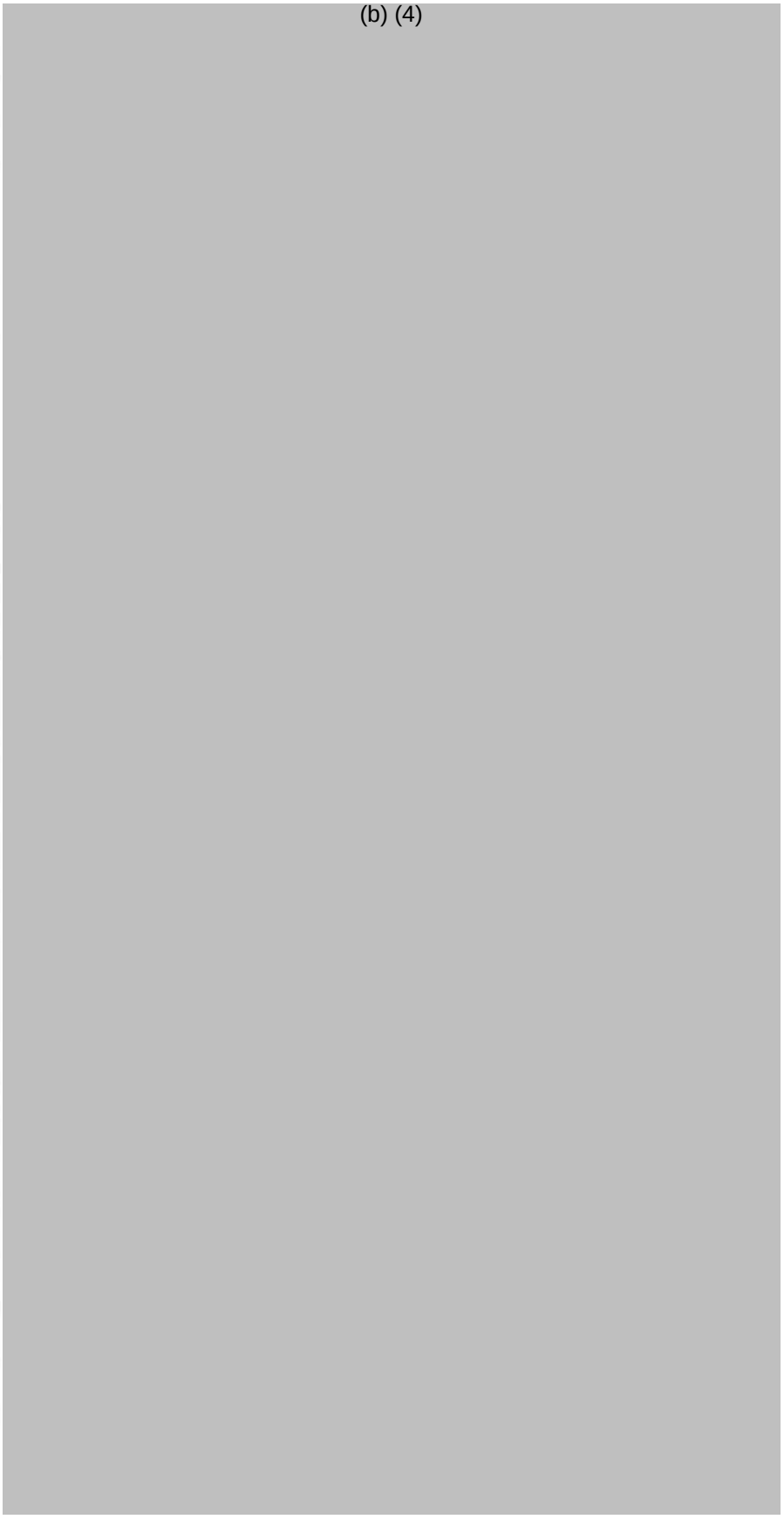
Vial Label:

1. Change “Tradename” to Halaven
2. The established name should be “(eribulin mesylate) injection”
3. Revise the statement of strength to read:

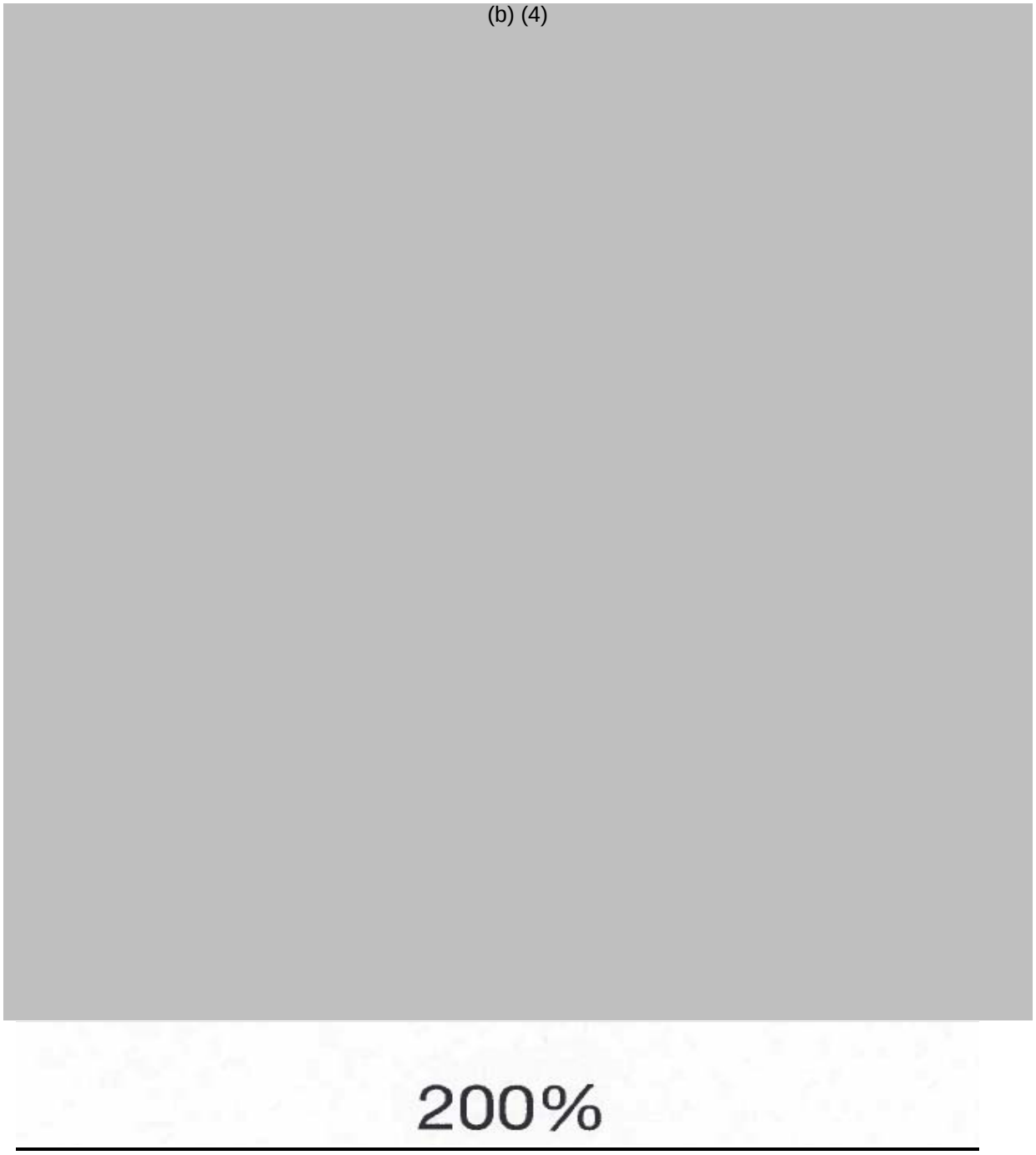
   1 mg/2 mL
   (0.5 mg/mL)
4. Relocate the statement of strength to the line below the established name.
5. Relocate the storage statement to the side of the panel.
6. The route of administration statement is not present. Place the route of administration statement, “For intravenous use”, below the strength.
7. Add “Sterile Solution”.
8. Add the statement “Single use vial—discard unused portion”
9. Revise the storage statement to “Store at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F). Do not freeze or refrigerate.
10. Add the statement, “Caution: Cytotoxic Agent” to the vial label.
11. Include the Lot number and expiration date.
12. 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.”

Eisai submitted the following revised carton and container label on July 23, 2010:

(b) (4)



(b) (4)



Following review, the additional DMEPA comments were sent to Eisai, on September 14, 2010:

1. Container Label and Carton Labeling

a. 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).

b. Present the route of administration statement in title case (i.e, "For Intravenous Use").

2. Carton Labeling

a. 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.

1) 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.

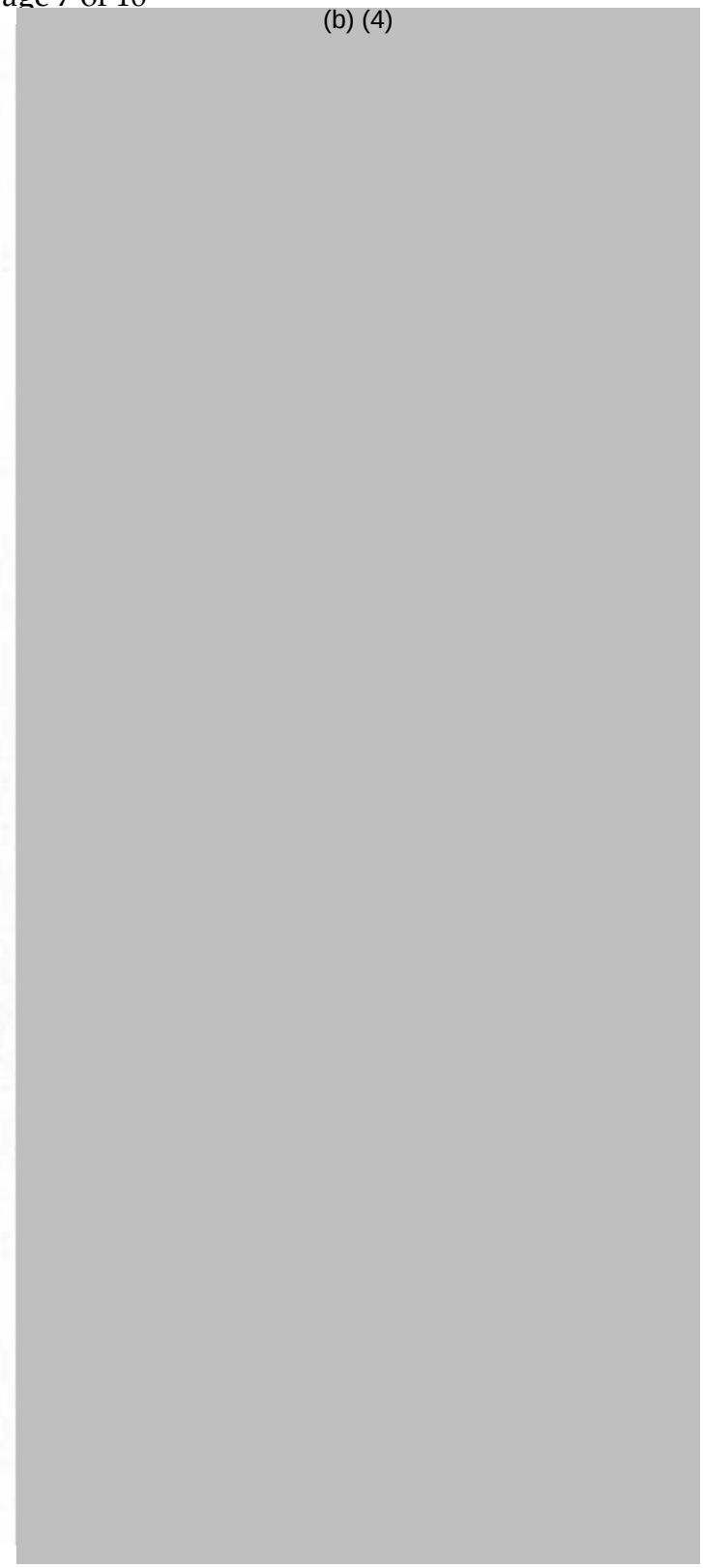
2) Align the statement of strength with the left margin of the proprietary name and established name as was done on the container label.

3) Relocate the statements "Sterile Solution" and "Caution: Cytoxic Agent" to the area below the route of administration.

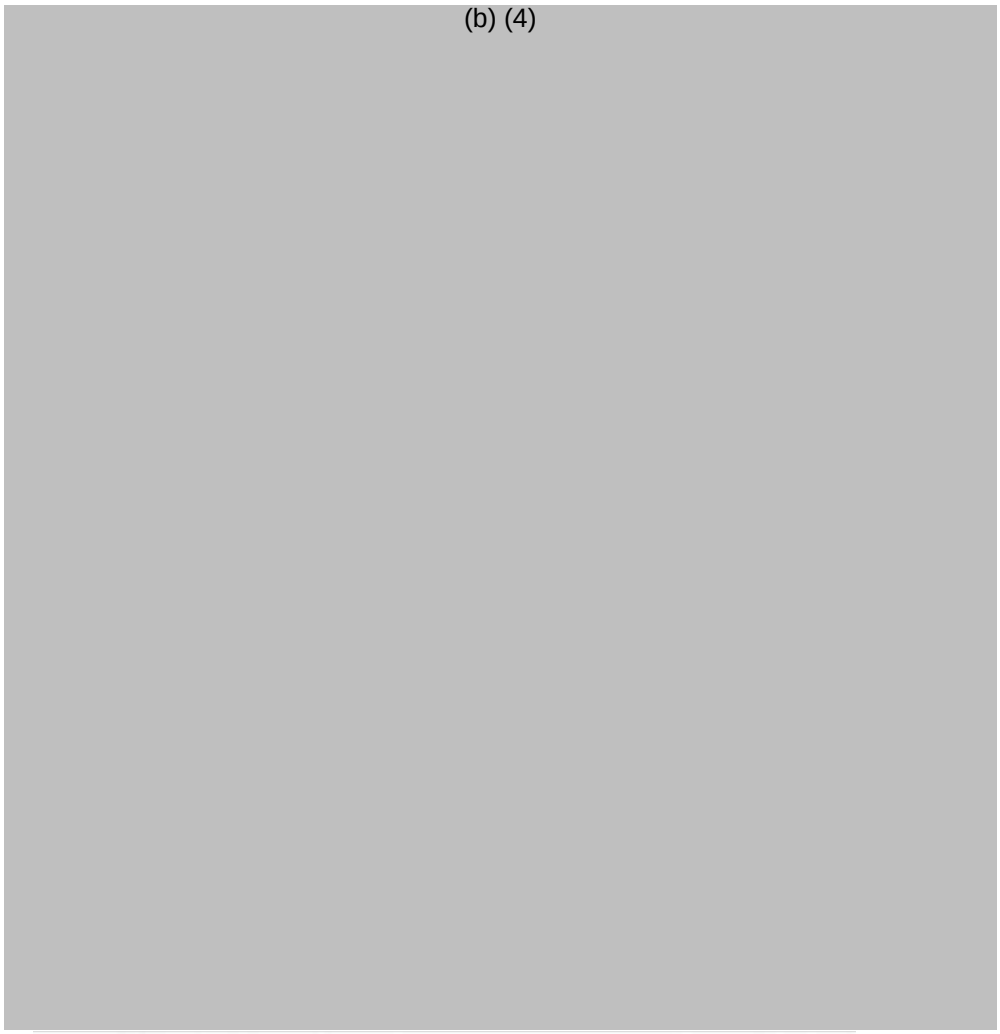
b. Increase the prominence of the statement "Single use vial—discard unused portion.

On September 23, 2010, Eisai responded with revised carton and container label:

(b) (4)



(b) (4)



Upon review DMEPA identified concerns with the revisions Eisai proposed for the container and carton labels. FDA issued the following comments to Eisai on September 24, 2010 via email:

Container Label

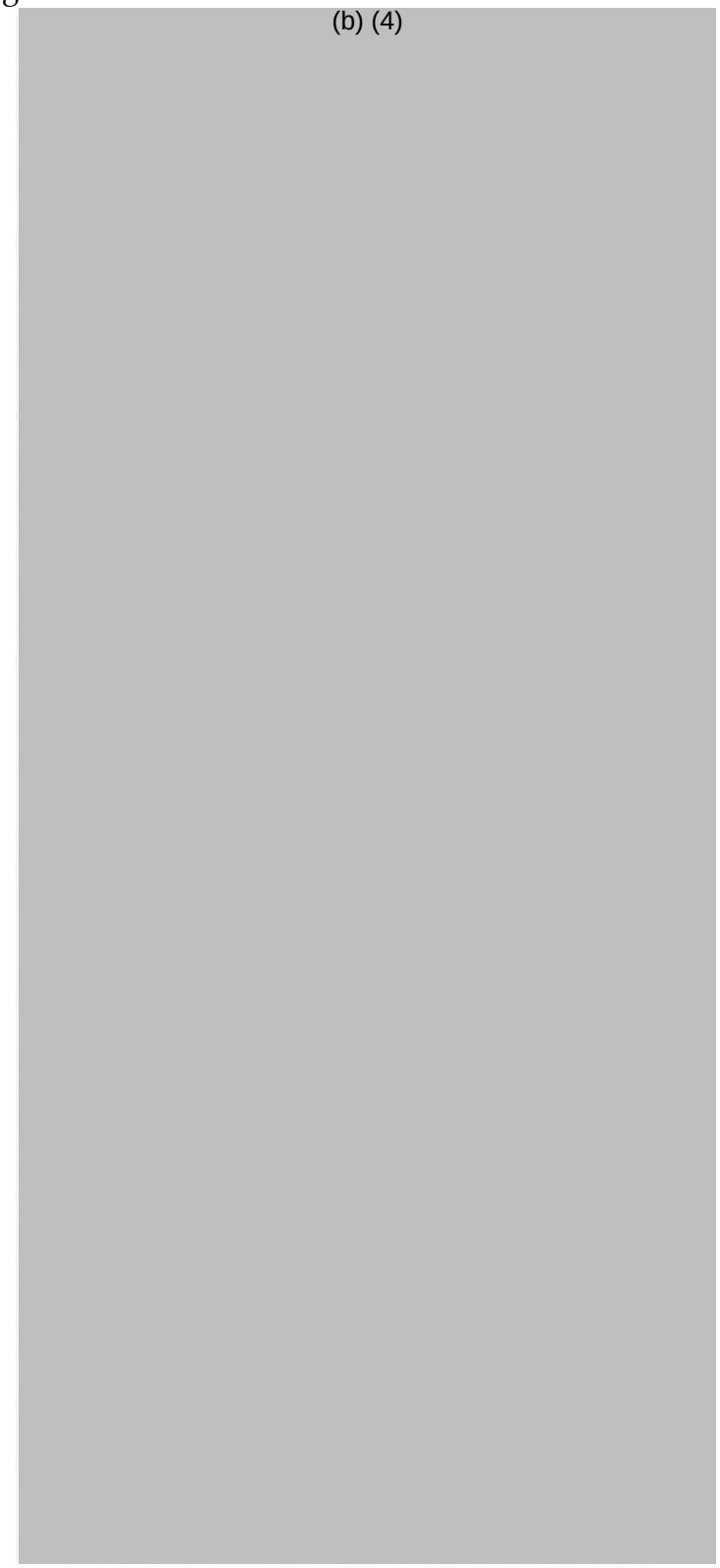
The "Rx only" statement is too prominent on the label. Relocate the "Rx only" statement to a less prominent area on the label (e.g., to the right of the NDC number) and decrease the font weight.

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).

To address FDA's concerns, on September 28, 2010, Eisai responded with the following revised carton and container label:

(b) (4)



(b) (4)

Subsequent to review Eisai's September 28, 2010 submission, FDA identified the following additional concerns.

1. The first letter of the dosage form should be capitalized, as it is part of the name.

2. The manufacturer is not consistently identified on the container, carton and package insert label, ie:

On the package Insert, the information is stated:

Manufactured by:
NerPharMa
Viale Pasteur, 10
20014, Nerviano
Italy

Distributed by:
Eisai Inc.
100 Tice Blvd. Woodcliff Lake, NJ 07677

On the carton, the information is stated:

(b) (4)

On the container, the information is stated:

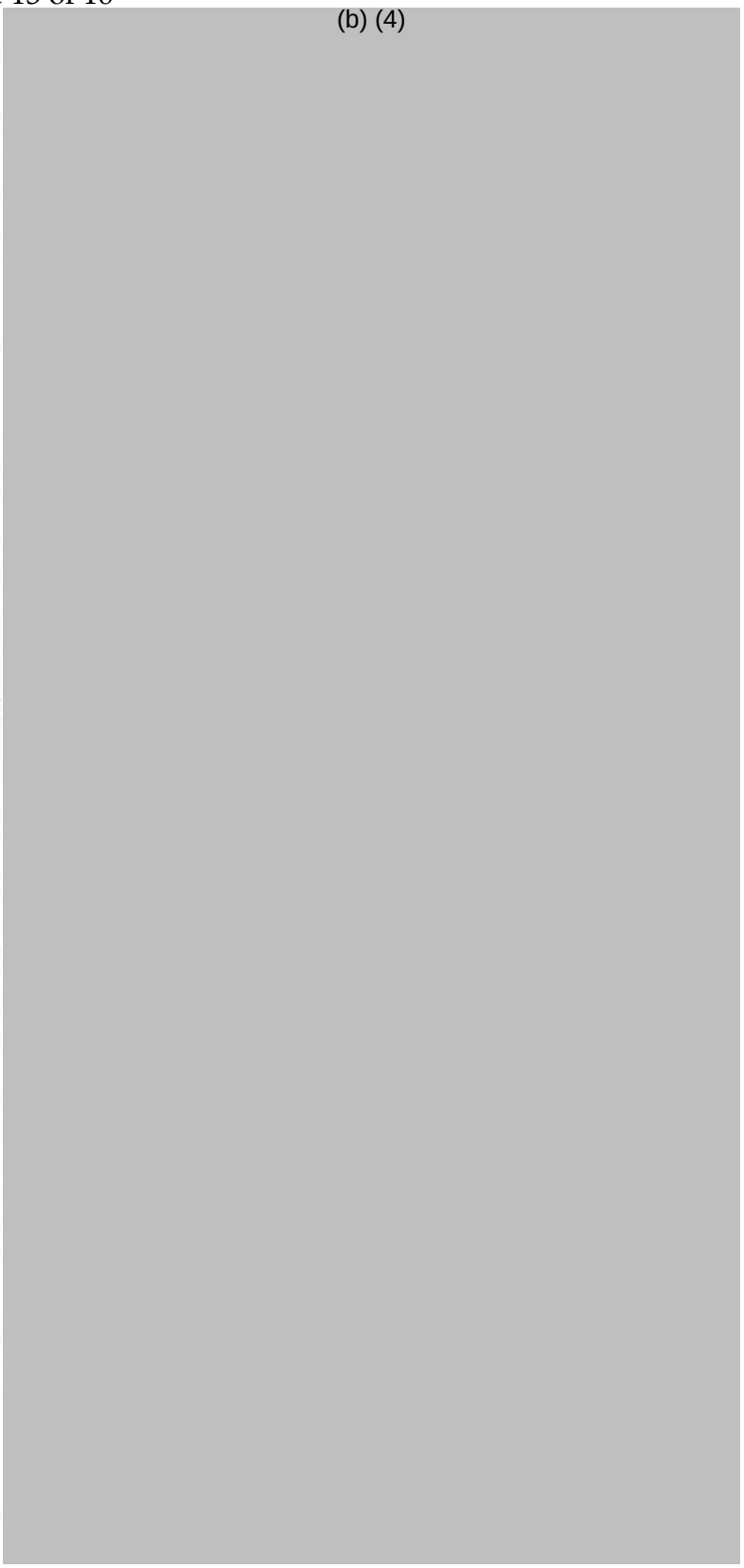
(b) (4)

On October 7, 2010, FDA requested that Eisai make the following changes:

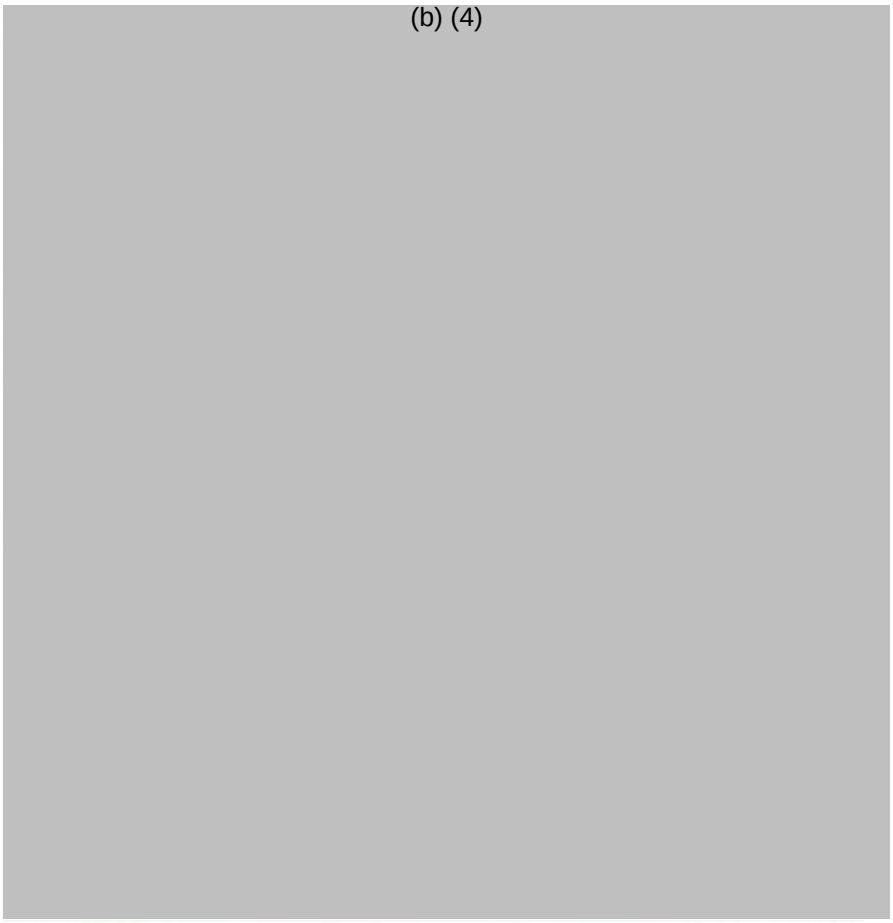
1) Capitalize the first letter of the dosage form as it is part of the name.
2) Display manufacturer/distributor information consistently on all the labels to prevent any potential confusion.

To address FDA's concerns, on October 13, 2019, Eisa responded with the following revised carton and container label:

(b) (4)



(b) (4)



Upon review, DBOP identified concerns with the revisions Eisai proposed for the container and carton labels and on October 17,2010, FDA requested that Eisai accommodate the full address, or at a minimum, the city, state and zip code in the carton labeling for manufacturer and distributor.

To address FDA's concerns, on October 27, 2010, Eisai responded with the following revised carton and container label:


Halaven™
(eribulin mesylate) Injection
1 mg/2 mL
(0.5 mg/mL)
For Intravenous Use
STERILE SOLUTION
CAUTION: Cytotoxic Agent
Rx only
202099

The revised container and carton labeling submitted by Eisai on October 27, 2010 is acceptable.

_____
Vaishali Jarral
Regulatory Project Manager
CDER/OODP/DBOP

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/s/

AZEEM D CHAUDHRY
11/08/2010

KAREN D JONES
11/08/2010

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Submission of prior approval supplement to include method of detection and acceptance criteria for starting materials and key intermediates

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	
Study/Clinical trial Completion Date:	
Final Report Submission Date:	03/31/2011
Other: /	

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

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

Increased survivability of clinical population affected by life threatening condition.

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

Sponsor (Eisai) commits to the following:

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 justificiation.

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.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

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

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Analytical method development and validation to quantify unspecified and specifed impurities in starting materials and key designated intermediates each with an acceptance criterion supported by manufacturing batch history. Methodology and resulting data package will be submitted in a prior approval supplement by 31 Mar 2011.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

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

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

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

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

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

_____
(signature line for BLAs)

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/s/

VAISHALI JARRAL
10/01/2010

JEFFERY L SUMMERS
10/01/2010

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Submit a final study report and datasets for trial E7389-G000-305, "EMBRACE' Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. 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 Brest Cancer , Previously Treated with At Least Two and Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	(b) (4)
Study/Clinical trial Completion Date:	
Final Report Submission Date:	MM/DD/YYYY
Other:	0/DD/YYYY

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

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

Study E7389-G000-305 is the primary study submitted in support of NDA 201532 for Halaven in the treatment of a lifethreatening illness, refractory metastatic breast cancer. The primary measurement of efficacy in this study is overall survival. At the time of the pre-specified data-cuttoff, 334 patients were still on-study and 33 patients remained on study therapy.
Long term data that reflects the outcomes of these remaining patients would enable a more complete assessment of the effectiveness of Halaven for the treatment of refractory metastatic breast cancer.

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

Please see the answer to Question 1.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Not applicable, please see above. This PMC is for submission of a datasets and a final report for registration study E7389-G000-305.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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

Agreed upon:

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

☒ Other
Submission of datasets and final study report upon completion of registration trial E7389-G000-305.

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

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

PMR/PMC Development Coordinator:

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

_____

(signature line for BLAs)

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

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/s/

VAISHALI JARRAL
09/15/2010

JEFFERY L SUMMERS
09/16/2010

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Impaired Renal Function

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	12/31/2010
	Study/Clinical trial Completion Date:	06/30/2012
	Final Report Submission Date:	12/31/2012
	Other:	MM/DD/YYYY

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

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

The major elimination pathway in humans is fecal (82% of dose; 88% as eribulin). Renal elimination (< 9%) and metabolism represents a minor contribution. A dedicated renal impairment study was not conducted, but a population PK analysis was conducted by the applicant. The Pharmacometrics population PK analysis indicates that a slight trend is observed between creatinine clearance (CLCR) and clearance (CL) for patients with mild and moderate renal impairment

We evaluated the dose-adjusted AUC for patients with normal renal function (n=44), and mild (n=27) and moderate (n=6) renal impairment enrolled into one of six dose clinical pharmacology trials with rich PK data. These patients are a subset of the population included in the population PK analyses. Our analysis demonstrated that the geometric mean dose-normalized AUC increased 2-fold in patients with moderate renal impairment. No patients with severe renal impairment were enrolled into the clinical trials included in this submission.

The applicant demonstrated that the probability of a patient experiencing Grade 4 neutropenia is associated with eribulin exposure and AST with an increasing probability of neutropenia with increasing eribulin systemic exposure and AST levels. Our analysis suggests a trend of increased incidence of grade 3-4 neutropenia and grade 3-4 febrile neutropenia with increasing exposure. The data is limited to exposure at one dose level from 169 patients enrolled into a phase 2 trial (study 211).

In a phase 1 clinical trial of eribulin in 15 patients with renal dysfunction and advanced urothelial cancer presented at the Annual Meeting of the American Society of Clinical Oncology 2010 in Chicago, Illinois, the investigators demonstrated that a trend towards increasing AUC and decreasing clearance with worsening renal function was found (Synold TW, et al. Am Soc Clin Oncol 2010; abstract #2527).

We recommend the sponsor conduct a clinical trial in patients with severe renal impairment. as compared to patietns with normal renal function to compare the systemic exposure of eribulin after receiving a single clinical dose.

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

The goal of the clinical trial is to (b) (4) for patients with severe renal impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

A clinical trial should be conducted 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. A single dose study is satisfactory. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
dedicated renal function study (see box 1)
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

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

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

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

(signature line for BLAs)

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

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/s/

VAISHALI JARRAL
09/15/2010

JEFFERY L SUMMERS
09/16/2010

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Submit datasets and a final study report for 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." .

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	(b) (4)
Study/Clinical trial Completion Date:	
Final Report Submission Date:	
Other:	0/DD/YYYY

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

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

Trial E7389-G000-305 demonstrated that Halaven therapy provides a clinically meaningful improvement in overall survival in patients with refractory, metastatic breast cancer, a life-threatening disease. Thus, approval of Halavan based on one adequate, well-controlled study is justified. Furthermore, requiring an additional trial (such as trial E7389-G000-301) to be completed prior to approving NDA 201532 would not be ethical, because it would delay giving patients with refractory metastatic breast cancer therapy that may be life-prolonging.

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

Assess outcomes of eribulin in a second study that is ongoing at the time of approval. The patient population differs in that patients in the E3789-G000-301 are capecitabine naïve and less heavily pretreated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Clinical Trial E7389-G000-301 is an ongoing clinical trial that is expected to be completed in (b) (4) Patient accrual for this study has been completed. This trial is investigating Halaven in patients with refractory metastatic breast cancer who have not received prior capecitabine therapy. This represents a less-heavily treated subgroup of patients than those enrolled in study E7389-G000-305, in which 73% of patients had received prior capecitabine therapy.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

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

_____

Agreed upon:

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

_____

☐ Other

_____

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

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

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

_____
(signature line for BLAs)

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

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/s/

VAISHALI JARRAL
09/15/2010

JEFFERY L SUMMERS
09/16/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 10, 2010
To:	Patricia Keegan, MD, Director Division of Biologic Oncology Products (DBOP)
Through:	Kristina A. Toliver, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Halaven (Eribulin Mesylate) Injection 1 mg/2 mL (0.5 mg/mL)
Application Type/Number:	NDA 201532
Applicant:	Eisai Inc.
OSE RCM #:	2010-754

Contents

1 INTRODUCTION

This review responds to a request from the Division of Biologic Oncology Products (DBOP) for DMEPA's assessment of the container label, carton labeling, and insert labeling for Halaven (Eribulin Mesylate) Injection 1 mg/2 mL (0.5 mg/mL), NDA 201532.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the draft container label, carton, and insert labeling submitted as part of the March 30, 2010 submission (see Appendices C and D). Additionally, DMEPA evaluated the revised container label and carton labeling submitted on July 23, 2010 (see Appendices E and F).

- Container Label
- Carton Labeling
- Insert Labeling (no image)

3 REGULATORY HISTORY

Recommendations from DMEPA concerning the container label and carton labeling were forwarded to the reviewer in the Office of New Drug Quality Assessment (ONDQA) for review on July 12, 2010. Subsequently, the collective DMEPA and ONDQA container label and carton labeling recommendations were communicated to DBOP in a labeling meeting held on July 13, 2010 and a consensus was reached. These recommendations were forwarded to the Applicant on July 14, 2010. See Appendix A for the combined DMEPA and ONDQA recommendations. The Applicant submitted revised container label and carton labeling on July 23, 2010.

Additionally, DMEPA had recommendations concerning the insert labeling which were also communicated to DBOP during the labeling meeting held on July 13, 2010 (see Appendix B).

4 RECOMMENDATIONS

Our evaluation noted areas where information on the July 23, 2010 revised container label and carton labeling can be improved to minimize the potential for medication errors.

We would be willing to meet with the Division of Biologic Oncology Products (DBOP) for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis (DMEPA) on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Sue Kang, at 301-796-4216.

4.1 COMMENTS TO THE APPLICANT

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: Cytoxic Agent" to the area below the route of administration.

2. Increase the prominence of the statement "Single use vial—discard unused portion.

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

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

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/s/

LORETTA HOLMES
09/10/2010

KRISTINA C ARNWINE
09/10/2010

DENISE P TOYER
09/10/2010

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Impaired Renal Function

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	12/31/2010
	Study/Clinical trial Completion Date:	06/30/2012
	Final Report Submission Date:	12/31/2012
	Other:	MM/DD/YYYY

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

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

The major elimination pathway in humans is fecal (82% of dose; 88% as eribulin). Renal elimination (< 9%) and metabolism represents a minor contribution. A dedicated renal impairment study was not conducted, but a population PK analysis was conducted by the applicant. The Pharmacometrics population PK analysis indicates that a slight trend is observed between creatinine clearance (CLCR) and clearance (CL) for patients with mild and moderate renal impairment

We evaluated the dose-adjusted AUC for patients with normal renal function (n=44), and mild (n=27) and moderate (n=6) renal impairment enrolled into one of six dose clinical pharmacology trials with rich PK data. These patients are a subset of the population included in the population PK analyses. Our analysis demonstrated that the geometric mean dose-normalized AUC increased 2-fold in patients with moderate renal impairment. No patients with severe renal impairment were enrolled into the clinical trials included in this submission.

The applicant demonstrated that the probability of a patient experiencing Grade 4 neutropenia is associated with eribulin exposure and AST with an increasing probability of neutropenia with increasing eribulin systemic exposure and AST levels. Our analysis suggests a trend of increased incidence of grade 3-4 neutropenia and grade 3-4 febrile neutropenia with increasing exposure. The data is limited to exposure at one dose level from 169 patients enrolled into a phase 2 trial (study 211).

In a phase 1 clinical trial of eribulin in 15 patients with renal dysfunction and advanced urothelial cancer presented at the Annual Meeting of the American Society of Clinical Oncology 2010 in Chicago, Illinois, the investigators demonstrated that a trend towards increasing AUC and decreasing clearance with worsening renal function was found (Synold TW, et al. Am Soc Clin Oncol 2010; abstract #2527).

We recommend the sponsor conduct a clinical trial in patients with severe renal impairment. as compared to patietns with normal renal function to compare the systemic exposure of eribulin after receiving a single clinical dose.

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

The goal of the clinical trial is to (b) (4) for patients with severe renal impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

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

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

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

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

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

A clinical trial should be conducted 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. A single dose study is satisfactory. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
dedicated renal function study (see box 1)
☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

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

☐ Other

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

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
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PMR/PMC Development Coordinator:
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(signature line for BLAs)

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

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/s/

VAISHALI JARRAL
09/08/2010

STACY S SHORD
09/10/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 2, 2010

TO: Vaishali Jarral, Regulatory Project Manager
Martha Donoghue, Medical Officer
Division of Biologic Oncology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 201532

APPLICANT: Eisai Medical Research Inc.

DRUG: Halaven (Eribulin Mesylate injection)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Halaven (eribulin mesylate injection) is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have received two or more chemotherapeutic regimens, including an anthracycline and a taxane.

CONSULTATION REQUEST DATE: 4/20/20010

DIVISION ACTION GOAL DATE: 9/30/2010; revised 12/30/2010 (Major Amendment received on 8/9/2010)

PDUFA DATE: 09/30/2010; revised 12/30/2010 (Major Amendment 8/9/2010)

I. BACKGROUND:

Eisai seeks approval of Halaven (eribulin mesylate injection) for the treatment of patients with locally advanced or metastatic breast cancer who have received two or more chemotherapeutic regimens, including an anthracycline and a taxane. The application is supported primarily by data from the pivotal phase III study, E7389-G000-305, the 'EMBRACE' Trial, entitled, "**E**isai **M**etastatic **Br**east Cancer Study **A**ssessing Physician's **C**hoice Versus **E**7389. A Phase III 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." This study was targeted for inspection. The data generated by this study are deemed critical by the review division in understanding the efficacy and safety parameters of eribulin mesylate injection for treatment of locally advanced or metastatic breast cancer. Eisai reports that eribulin mesylate demonstrated a statistically significant improvement ($p = 0.041$) in Overall Survival (OS), the primary endpoint of Study 305, compared with the control group, Treatment of Physician's Choice. Treatment of Physician's Choice was defined as any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, administered according to local practice.

Five clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Javier Cortes (site number 2008), Dr. Philippe Bougnoux (site number 1401), Dr. Thierry Delozier (site number 1402), Dr. Joanne Blum (site number 2815), and Dr. Han Koh (site number 2812). These sites were selected for inspection because several had substantial protocol violations that may be pertinent to efficacy analysis, most notably major inclusion criteria protocol deviations. In addition, each site reported a high rate of treatment responders to the test article, and all had relatively high enrollment numbers. Finally, there are insufficient domestic data. The study sponsor, Eisai, and a CRO, (b) (4), were inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Site #2008 – Dr. Javier Cortes Hospital Vall d'Hebron Unitat de cancer de mama, planta 1, Edifici Materno-Infantil Paseo Vall d'Hebron, 119-120 08035 Barcelona Spain	Protocol: E7389-G000-305 [EMBRACE] Site Number: 2008 Number of Subjects: 34	7/26/2010 – 7/30/2010	Pending Interim classification: VAI
CI#2: Site #1401 – Dr. Philippe Bougnoux Hopital Bretonneau Service CORAD 2 Boulevard Tonnelle	Protocol: E7389-G000-305 [EMBRACE] Site Number: 1401	7/19/2010 – 7/22/2010	Pending Interim classification: VAI

Name of CI or Sponsor/CRO, Location	**Protocol #: and # of Subjects:**	**Inspection Date**	**Final Classification**
37044 Tours Cedex France	Number of Subjects: 17		
CI#3: Site #1402 – Dr. Thierry Delozier Centre Francois Baclesse Caen Avenue Du General Harris BP 5026 14076 Caen Cedex 05 France	Protocol: E7389-G000-305 [EMBRACE] Site Number: 1402 Number of Subjects: 19	7/12/2010 – 7/16/2010	Pending Interim classification: VAI
CI#4: Site #2815 – Dr. Joanne L. Blum US Oncology 3535 Worth Street Sammons Cancer Center Collins Building Dallas, Texas 75246	Protocol: E7389-G000-305 [EMBRACE] Site Number: 2815 Number of Subjects: 21	6/29/2010 – 7/2/2010, 7/6/2010 – 7/9/2010, 7/13/2010	Pending Interim classification: VAI
CI#5: Site #2812 – Dr. Han A. Koh Bellflower Satellite 9400 East Rosecrans Avenue Module 3200 Kaiser Permanente – Bellflower Bellflower, CA 90706	Protocol: E7389-G000-305 [EMBRACE] Site Number: 2812 Number of Subjects: 18	6/21/2010 – 7/1/2010	Pending Interim classification: NAI
CRO: (b) (4) (b) (4)	Protocol: E7389-G000-305 [EMBRACE] Sites: 2008, 1402, 1402, 2815, 2812, 1901, 3011, 2503, 1302, 2304, 2604, 2911, 2907, and 2818.	7/26/2010 – 7/30/2010	Pending Interim classification: VAI
Sponsor: Eisai Limited (UK) European Knowledge Centre Mosquito Way Hatfield Herfordshire AL10 9SN United Kingdom	Study: E7389-G000-305 [EMBRACE] Sites: 2008, 1401, 1402, 2812, 2815, 1901, 3011, 2503, 1302, 2304, 2604, 2911, and 2907	July 19-23, 2010	Pending Interim classification: VAI

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

1. **CI#1:** Dr. Javier Cortes
(Site Number 2008)
Hospital Vall d'Hebron
Unitat de cancer de mama,
planta 1, Edifici Materno-Infantil
Paseo Vall d'Hebron, 119-120
08035 Barcelona Spain

   a. **What was inspected**: The site screened 42 subjects, 34 of those were randomized and treated. The study records of 25 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

      Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

   b. **General observations/commentary**: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting AEs. However, there were multiple instances where protocol-specified assessments were not done, several subjects (#1031 and #1036) were randomized but did not meet study entry criteria, and the site failed to maintain adequate records pertaining to drug accountability and in one instance source records for Subject #1002.

      Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 201532. A Form FDA 483 was issued to the clinical investigator citing 3 inspectional observations.

      Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

      1. Specifically, the following scheduled assessments (e.g. bone scan, physical examination, laboratory assessments, ECOG, vital signs and ECG) were not conducted in accordance with EMBRACE study Protocol E7389-G000-305 for study Site no. 2008. Note that the specific study visits that were impacted are titled as "C_D_" for Cycle and Day.

Subject No.	Tumor Assessment	Physical Exam	Laboratory Assessments*	ECG	Vital Signs	ECOG
1002			Urinalysis at C2D1, Study termination	Study termination	Study termination	
1003			C1D1			
1005				Study termination	Study termination	
1007		C2D8		Study termination	Study termination	C2D1
1008			C2D1	C2D1	C1D1, C2D1	C2D1
1012		C3D8			Weight, C2D1	
1013	Bone Scan (Radio-isotope) before start of study treatment					
1015				Study termination		
1016			Urinalysis C3D1;CBC C3D8			
1027				Study termination		
1031				C2D1		
1034				Study termination	Study termination	
1035				Study termination		
1037				Study termination		
1038		C1D8			C1D8, C2D1, C3D1, C4D1, C5D1, C6D1, C7D1	

C – Cycle
D – Day
* – At the time this CIS was written DSI had no additional information available regarding the listed missed laboratory assessments. Therefore, the following conservative assumptions are in effect until a review of the Establishment Inspection Report can be completed. When a specific laboratory assessment is identified in the Table (such as urinalysis) then this is the only laboratory assessment missed for that subject's cycle and day visit. When only a Cycle and Day are listed (i.e., C2D1) then it may be assumed that no protocol-specified laboratory assessments were conducted for that subject.

2. Specifically, the following subjects who failed to meet the inclusion criteria were randomized into the EMBRACE study for study Site no. 2008.

a. Subject 1031 - Elevated serum alkaline phosphatase (549) at screening.
b. Subject 1036 - Elevated serum alkaline phosphatase (398) at screening.

Observation 2: Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.

Specifically, drug accountability records for 10 subjects (1005,1011,1013,1015,1022, 1024,1027,1035,1040, and 1041) lacked destruction certification for unused study drug.

Observation 3: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, medical records or source documents including that of the physicians progress notes for Subject 1002 was missing. The study data (e.g. PE, ECOG, height, weight and body surface area calculations) entered into the CRF could not be verified.

DSI reviewer's Notes: DSI reviewer Lauren Iacono-Connors presented and discussed all of the inspectional findings above with the review division (DBOP) Medical Officer, Dr. Martha Donoghue. The DSI reviewer and DBOP MO agree that while "overall sloppiness" is disturbing from a protocol compliance standpoint, that the specific findings discussed above are unlikely to have significant impact on safety analyses, as the missing items as outlined in the table above were not pervasive findings for each study visit. Additionally, the Review Division MO concurs that the findings listed above are unlikely to significantly impact data integrity of the primary efficacy endpoint of OS. The review division may wish to consider the impact of these inspectional observations on other study analyses including secondary efficacy endpoints.

c. Assessment of data integrity: Not withstanding the regulatory violations noted above, the data for Dr. Cortes' site, associated with Study EMBRACE submitted to the Agency in support of NDA 201532, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

2. CI#2: Dr. Philippe Bougnoux
(Site Number 1401)
Hopital Bretonneau
Service CORAD
2 Boulevard Tonnelle
37044 Tours Cedex
France

a. What was inspected: The site screened 18 subjects, 17 of those were randomized and treated. The study records of 17 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison

of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting AEs. However, there were multiple instances where protocol-specified assessments were not done.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 201532. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, the following scheduled assessments (e.g. physical examination, laboratory assessments, ECOG, vital signs and ECG) were not conducted in accordance with EMBRACE study protocol E7389-G000-305 for study Site no. 1401. Note that the specific study visits that were impacted are titled as "C_D_" for Cycle and Day.

Subject No.	Physical Exam	Laboratory Assessments*	ECOG	Vital Signs	ECG
1001	C3D1		C3D1	Temperature C2D8, C3D1, C3D6,C4D8	
1002		C5D8			
1003		CBC C1D1, Chem C1D1, Urinalysis C1D1, Chemistry C2D15		Temperature C2D15, Vital sings at study termination	C1D1, C2D1
1004		Chemistry C1D1, C1D8, C2D15, C3D1, C4D8, C7D8, C8D1,			C2D1

Subject No.	Physical Exam	Laboratory Assessments*	ECOG	Vital Signs	ECG
		C8D8, C9D1, C10D1, C11D1, C11D8			
1005	C3D1, C3D8, C4D1, C4D8, study termination	C1D1, C1D15, C3D1, C5D1, C4D8, C5D1, C6D8, C9D1, C9D8, C11D8, C12D1			C2D1, study termination
1007		C2D8, C3D1		Study termination	Study termination
1008	C2D1	C1D8, C2D1, C2D8, C4D1			Study termination
1010		C5D1, C8D8, C9D8, C10D8, C11D1, C11D8, study termination			Study termination
1011		C1D8, C2D8, C3D1, C3D8,	Study termination	Study termination	Study termination
1012		C3D8, C5D1, C6D8, C10D1, C5D8, C7D8, C10D8, C11D1, C11D8		C1D8, Study termination	
1013	C2D8, C3D8, C4D8, C6D8	C2D1, C4D1, C3D1, C4D8, C5D1, C6D1, C7D1		C1D1	
1015	C1D1, C2D8, C3D8	C2D1, C3D1, study termination	Study termination		
1016	C1D1, C1D8, C2D8, C3D8, C4D8, C5D8, C6D1, C6D8		C1D1, C6D1	C2D8, C3D8, C4D8, C5D1, C5D8, C7D1	C2D1, study termination
1017	C1D8, C6D8	C1D8, C2D1, C2D8, C3D1	Study termination	Study termination	
1018		C1D1, C2D8, C3D1, C4D1, C4D8, study termination		C1D8, C1D15, C3D8, study termination	Study termination

C – Cycle
D – Day
* – At the time this CIS was written DSI had no additional information available regarding the listed missed laboratory assessments. Therefore, the following

conservative assumptions are in effect until a review of the Establishment Inspection Report can be completed. When a specific laboratory assessment is identified in the Table (such as urinalysis) then this is the only laboratory assessment missed for that subject's cycle and day visit. When only a Cycle and Day are listed (i.e., C2D1) then it may be assumed that no protocol-specified laboratory assessments were conducted for that subject.

DSI reviewer's Notes: DSI reviewer Lauren Iacono-Connors presented and discussed all of the inspectional findings with the review division (DBOP) Medical Officer, Dr. Martha Donoghue. The DSI reviewer and DBOP MO agree that while "overall sloppiness" is disturbing from a protocol compliance standpoint, that they are unlikely to significantly impact the safety analyses. Additionally, the Review Division MO also concurs that the findings listed above are unlikely to significantly impact data integrity of the primary efficacy endpoint of OS. The review division may wish to consider the impact of these inspectional observations on other study analyses including secondary efficacy endpoints.

c. Assessment of data integrity: Not withstanding the regulatory violations noted above, the data for Dr. Bougnoux's site, associated with Study EMBRACE submitted to the Agency in support of NDA 201532, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

3. CI#3: Dr. Thierry Delozier
(Site Number 1402)
Centre Francois Baclesse Caen
Avenue Du General Harris
BP 5026
14076 Caen Cedex 05
France

a. What was inspected: The site screened 23 subjects, 19 of those were randomized and treated. The study records of 16 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subjects' records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting AEs. However, there were multiple instances where protocol-specified assessments were not done. In addition, the site failed to maintain adequate records pertaining to infusion records (CRF). Infusion records did not always record the start/stop times and volume infused, as required by the protocol.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 201532. A Form FDA 483 was issued to the clinical investigator citing 2 inspectional observations.

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, the following scheduled assessments (e.g. physical examination, laboratory assessments, ECOG, vital signs and ECG) were not conducted in accordance with EMBRACE study protocol E7389-G000-305 for study Site no. 1402. Note that the specific study visits that were impacted are titled as "C_D_" for Cycle and Day.

Subject No.	Physical Exam	Laboratory Assessments*	ECOG	Vital Signs	ECG
1004	C1D1, C1D8, C1D15, C2D8, C2D15, C3D1, C3D8, C4D8, C4D15, C5D1, C5D8, C5D15, C6D15, C7D8, C8D1, C8D15	Urinalysis, pH, sp. Gravity at C13D1, C14D1, C15D1, C16D1	C13D1, C16D1		Study termination
1006	C1D1				
1008	C1D8	C1D1		Study termination	
1009	C2D8, C3D1, C3D8, C4D1	Albumin, T. Protein, Phosp, Mg at screening; urinalysis at C1D1 and at study termination	C1D1, C3D1	Study termination	Study termination
1010	C1D1, C1D15, C4D15				

1013	C1D8, C3D8, C1D15, C3D1, C4D8, C5D8				
1014	C4D8		C2D1, C8D1	C2D15, study termination	
1015	C1D1		C1D1, C3D1		
1018	C1D1		C4D1		C2D1
1019	C1D1, C2D2, C2D8, C2D15, C3D8				
1020		C1D1	C2D2		
1022		C1D1, C2D1, C4D1		C4D8	
1023	C1D1, C2D8		C3D1		C2D1

C – Cycle
D – Day
* – At the time this CIS was written DSI had no additional information available regarding the listed missed laboratory assessments. Therefore, the following conservative assumptions are in effect until a review of the Establishment Inspection Report can be completed. When a specific laboratory assessment is identified in the Table (such as urinalysis) then this is the only laboratory assessment missed for that subject's cycle and day visit. When only a Cycle and Day are listed (i.e., C2D1) then it may be assumed that no protocol-specified laboratory assessments were conducted for that subject.

Observation 2: Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

Specifically, Subjects 1006, 1008, 1009, 1010, 1013, 1015, 1018, 1020, and 1023, had at least one infusion record (Case Report Form) that was not properly completed (start/stop times and volume infused).

DSI reviewer's Notes: DSI reviewer Lauren Iacono-Connors presented and discussed all of the inspectional findings above with the review division (DBOP) Medical Officer, Dr. Martha Donoghue. The DSI reviewer and DBOP MO agree that while "overall sloppiness" is disturbing from a protocol compliance standpoint, that the findings are unlikely to significantly impact safety analyses. Additionally, the Review Division MO also concurs that the findings listed above are unlikely to significantly impact data integrity of the primary efficacy endpoint of OS. The review division may wish to consider the impact of these inspectional observations on other study analyses including secondary efficacy endpoints.

c. Assessment of data integrity: Not withstanding the regulatory violations noted above, the data for Dr. Delozier's site, associated with Study EMBRACE submitted to the Agency in support of NDA 201532, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

4. CI#4: Dr. Joanne L. Blum
(Site Number 2815)
US Oncology
3535 Worth Street
Sammons Cancer Center
Collins Building
Dallas, Texas 75246

a. What was inspected: The site screened 26 subjects, 21 of those were randomized and treated. The study records of 21 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subjects' records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data were verifiable. However, the site had protocol deviations consisting of not reporting or misreporting AEs, missing laboratory assessments and missing study windows. Protocol deviation forms did not reflect the incident occurrence date and did not have proper corrective action documented.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 201532. A Form FDA 483 was issued to the clinical investigator citing 2 inspectional observations.

Observation 1: An investigation was not conducted in accordance with the investigational plan.

Specifically,

1. The protocol states in Section 11.1 Adverse Events, Severity, and Relationship that "Adverse Events in clinical investigation subjects include any change in the

subject's condition." This definition includes symptoms, physical findings, or clinical syndromes, and abnormal laboratory values.

a. For 4 of the 21 subjects reviewed (1001, 1005, 1006, 1014), hypomagnesemia was observed but was not reported as an adverse event. However, the site identified and reported hypomagnesemia as an adverse event for Subjects 1015 and 1016.

   For Subject 1021, hypomagnesemia was reported as an adverse event but it occurred prior to the enrollment date of April 28, 2008, and should have been considered medical history.

b. Subject 1020 experienced low absolute neutrophil count on April 22, 2008. This was after the subject signed the informed consent on April 22, 2008. According to the protocol, Section 11.1, all adverse events should be reported from the time the subject signs the informed consent.

c. Subject 1019 experienced low absolute neutrophil count on July 24, 2008. This was not reported as an adverse event.

d. For subject 1007 "heart skipping" was reported on August 16, 2007. An electrocardiogram and a heart monitor were reportedly ordered for this subject. No results from these exams were observed in the subject study records and no adverse event was submitted. No further information was provided by the firm.

2. Failure to perform a urinalysis assessment as required by the protocol for the following subjects: on October 25, 2007, Cycle 1, Day 3 for Subject 1009 and on the screening visit for Subject 1001.

3. For Subject 1010 and Subject 1022, the screening assessments were conducted outside of the 14-day window prior to treatment. For Subject 1010, the informed consent was signed on September 25, 2007 and Cycle 1, Day was on October 11, 2007. For Subject 1022, the screening laboratory assessments were completed on May 9, 2008 and cycle 1, day 1 was May 23, 2008.

4. According to the protocol, section 8.6.1, the test article is to be administered in an IV bolus over 2 to 5 minutes. For Subject 1019, test article was reportedly administered for 10 minutes on both cycle 2, day 1 (April 10, 2008) and cycle 2, day 8 (April 17, 2008).

Observation 2: Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically, "Protocol Deviation Forms" do not properly reflect the specific details of the incident or the plan or action to prevent the deviation from reoccurring. For example, for 16 of 17 subjects for which protocol deviations forms were submitted and reviewed, the "Plan of Action" for the incident to be prevented was reported as "Adhere to Protocol". As a result, several of these protocol deviations reoccurred throughout the study, such as lab assessments not being performed and times vital signs were taken were not documented. In addition, under the section of the Protocol Deviation Form for "Specific Details of Incident (including cycle # and dates)" the date and cycle number was omitted from several protocol deviation forms submitted for 11 of 17 subjects.

c. Assessment of data integrity: Although regulatory violations were noted, these are considered unlikely to significantly impact data reliability. The data for Dr. Blum's site, associated with EMBRACE Study submitted to the Agency in support of NDA 201532, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

5. CI#5: Dr. Han A. Koh
(Site Number 2812)
Bellflower Satellite
9400 East Rosecrans Avenue
Module 3200
Kaiser Permanente – Bellflower
Bellflower, CA 90706

a. What was inspected: The site screened 31 subjects, 18 of those were randomized and treated. The study records of 18 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be good. The records were very well organized. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subjects' records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. Primary efficacy endpoint data

were verifiable. However, the site had a few minor protocol deviations consisting of missing laboratory assessments; but there was no visible trend.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 201532. No Form FDA 483 was issued.

c. Assessment of data integrity: The data for Dr. Koh's site, associated with EMBRACE Study submitted to the Agency in support of NDA 201532, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

6. CRO: (b) (4)
(b) (4)

a. What was inspected: The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The study was conducted at 135 Centers in 19 countries and enrolled 762 subjects. The CRO was responsible for all monitoring (but not selection of monitors), data collection, and statistical analyses. This inspection was primarily focused on monitoring activities and the qualifications of the monitors. Coverage was also given to safety reports and data management.

N**ote:** The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: This inspection of (b) (4) revealed that this CRO location houses contract clinical study management personnel. Responsibility for monitoring was transferred to (b) (4). (b) (4) was also responsible for disseminating information to investigators under the terms of the written agreement. (b) (4) office was responsible for all data entry and record retention during the trial. (b) (4) provided statistical analysis and created all tables, listings and graphs in the final Clinical Study Report. (b) (4) work was verified by the study sponsor, Eisai.

This inspection included review of the CRO's study related documents for the following 14 sites: 2008, 1402, 1402, 2815, 2812, 1901, 3011, 2503, 1302, 2304, 2604, 2911, 2907, and 2818. This includes the five sites assigned for FDA inspection, eight other sites selected which were not audited by either FDA or the Sponsor, and one other U.S. Oncology site since those sites did not have site selection or initiation visits. U.S. Oncology sites were trained via conference call and initially had a number of deficiencies.

The FDA field investigator noted certain deficiencies in site monitoring. Specifically, monitoring during most of the active enrollment/treatment phase failed to meet the terms of the contract (Section 3.2 Interim Monitoring Visits) with the sponsor; that sites were to be visited within two weeks of the first subject enrolled and monitoring reports were to be provided within 15 days of a monitoring visit. According the FDA field investigator the Sponsor and (b) (4) met and agreed to bring on more CRAs but (b) (4) was unable to find additional CRAs meeting the experience requirements outlined in the monitoring plan. Each monitor's credentials were reviewed and each was approved by the sponsor. By late 2008, the CRO was able to get caught up with submission of monitoring reports.

Current monitoring and reporting appear to be in compliance. At the time that these reports were not being submitted on schedule, the Sponsor and CRO both explained that urgent issues were still being handled in a timely manner via their conference calls and e-mail correspondence.

There were no significant differences in the quality of the monitoring as evidenced by the monitoring reports. Investigator compliance issues were addressed through retraining and in some cases the sponsor decided not to continue enrollment at sites when the protocol was amended. SAEs from monitoring reports were verified for all subjects. All AE CRFs were requested and compared to the line listings for Sites 1302, 2604, and 2907. No significant deficiencies were noted. Finally, OS at the time of database lock for Sites 1901, 3011, 2503, 1302, 2304, 2604, 2911, and 2907 was verified against CRFs during the sponsor audit and for Sites 2818, 2008, 1401, 1402, 2815 and 2812 OS was verified during this inspection of (b) (4)

A Form FDA 483 was issued to the CRO citing 1 inspectional observation related to Monitoring deficiencies.

Observation 1: Failure to ensure proper monitoring of the study in accordance with the protocol and investigation plan.

Specifically, of the 14 investigator sites reviewed:

1. Eight did not have a monitoring visit within two weeks of randomization (2008, 2815, 2812, 3011, 1302, 2503, 2304 and 2818);
2. Monitoring Visit Reports were routinely submitted to the sponsor after the

specified 15 business days of the visit; and
3. Records were not available to document sponsor notification of investigator availability issues with respect to Site 2815 in 2007 and 2008.

According to the FDA field investigator, (b) (4) indicated they intend to respond to the Form FDA 483 in writing.

c. Assessment of data integrity: Although some deficiencies with respect to monitoring responsibilities were noted as described above, these deficiencies do not appear to have resulted in significant issues with sites' conduct of the clinical investigations, and are unlikely to impact data reliability. The data generated at this site, as it pertains to Study EMBRACE were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this CRO submitted to the agency as part and in support of NDA 201532 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

7. Sponsor: Eisai Limited (UK)
European Knowledge Centre
Mosquito Way
Hatfield
Herfordshire
AL10 9SN
United Kingdom

a. What was inspected: The sponsor was inspected completing the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The study was conducted at 135 Centers in 19 countries and enrolled 762 subjects. Specifically, the inspection covered adherence to Protocol EMBRACE, and review of the firm's SOPs, including monitoring SOPs, Ethics Committee/IRB approvals, completed Form FDA 1572s, monitoring reports, communications with the sites, subjects' randomization, drug accountability and review of data management from the clinical study sites to the submission of the NDA to the Agency.

This inspection was primarily focused on monitoring activities and the qualifications of the monitors. Coverage was also given to quality assurance, pharmacovigilance, and the clinical supply system. To the extent possible, biostatistics and data management systems were evaluated for quality processes and controls as outlined in the written policies and study procedures. Verification activities performed upon receipt of data from the CRO were also reviewed.

The qualifications for monitors assigned to thirteen sites (Site numbers 2008, 1401, 1402, 2812, 2815, 1901, 3011, 2503, 1302, 2304, 2604, 2911, and 2907) were assessed. These sites included the five sites assigned for FDA inspection and eight others which

had not been audited by FDA or the Sponsor's QA Unit.

N**ote:** The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: This was the initial inspection of Eisai Limited and the European Knowledge Centre, a facility that opened in 2009. Eisai Limited is the United Kingdom Affiliate of Eisai Europe Limited, a European holding company owned by Eisai Company, Limited of Japan. Also held by Eisai Europe, Limited is Eisai Manufacturing Limited, the European manufacturing operation. Eisai Co., Ltd. is the parent company of Eisai Corporation of North America, which was incorporated in the United States in 1995. For the conduct of clinical research projects, the company organizes employees' activities across corporations in what are termed Product Creation Units (PCUs) and Core Function Units (CFUs). In the case of the audited study, members of the Oncology PCU and the Scientific Operations and Clinical Support CFU collaborated on the project.

This initial inspection of Eisai Limited revealed that this location houses clinical study management personnel and a finished dosage (b) (4) form production facility. The firm used numerous CROs for conducting the study, in particular (b) (4) was contracted to perform clinical monitoring, data collection, and statistical analyses. Responsibility for monitoring was transferred by contract to (b) (4) but not the selection of monitors. (b) (4) was also responsible for disseminating information to investigators under the terms of the written agreement. (b) (4) was also responsible for all data entry and record retention during the trial but these responsibilities were not officially transferred. (b) (4) provided statistical analysis and created all tables, listings and graphs in the final Clinical Study Report. (b) (4) work was verified by Eisai.

Verification activities performed upon receipt of data from the CRO were reviewed and found to be adequate. Written procedures for monitoring, data management and oversight of contractors were reviewed and no objectionable conditions were noted.

The primary efficacy endpoint (Overall Survival) for Sites 1901, 3011, 2503, 1302, 2304, 2604, 2911, and 2907 was verified against CRFs during this audit. (OS for Sites 2818, 2008, 1401, 1402, 2815 and 2812 were verified during the inspection of the CRO.) No errors were noted. While monitoring activities failed to meet the terms of the CRO agreement with the Sponsor and the conditions outlined in the protocol, assessed reports indicate that oversight of all reviewed sites was adequate. No evidence suggested a lack of reliability of efficacy data or significant underreporting of safety data.

At the conclusion of the inspection, an FDA-483, Inspectional Observations form, was issued to management for deficiencies in monitoring and in the selection of monitors. A Form FDA 483 was issued to the Sponsor citing 2 inspectional observations.

Observation 1: Failure to ensure proper monitoring of the study in accordance with the protocol and investigation plan.

Specifically, of the 13 investigator sites reviewed:

1. Seven did not have a monitoring visit within two weeks of the first dose (2008, 2815, 2812, 3011, 2503, 2304, and 1302;
2. Monitoring Visit Reports were routinely submitted to the sponsor after the specified 15 business days of the visit; and
3. Telephone logs were not available to document sponsor notification of significant compliance issues with respect to Site 2604;
4. Less than 20% of the Monitoring Visit Reports were reviewed for sites outside of the Americas.

Observation 2: Monitors not qualified by experience and training were selected to monitor progress of a clinical investigation.

Specifically, in the sample of 13 investigator sites selected for evaluation, the sponsor was unable to provide documentation of monitor qualifications for the majority of the associates who performed monitoring of those sites.

According to the FDA field investigator, Eisai indicated they intend to respond to the Form FDA 483 in writing.

DSI reviewer's Notes: Based on available information, the sponsor would not be held responsible for monitoring deficiencies listed above, in part, inspectional observation 1, because this sponsor responsibility was contractually transferred to (b) (4)

c. Assessment of data integrity: The data generated at this site, as it pertains to Study EMBRACE were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this Sponsor location submitted to the agency as part and in support of NDA 201532 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Blum, Dr. Cortes, Dr. Koh, Dr. Bougnoux, and Dr. Thierry, a study CRO (b) (4), and

study sponsor, Eisai, the study data collected appear reliable. All inspected entities, with the exception of Dr. Koh, were issued a Form FDA 483 citing inspection observations.

A Form FDA 483 was issued to Dr. Blum noting protocol deviations consisting of not reporting or misreporting AEs, missing laboratory assessments and missing study windows. However, it does not appear that these inspectional observations were systemic. These observations should not impact overall integrity of site-generated data.

The inspections of Dr. Cortes, Dr. Bougnoux and Dr. Thierry, each resulted in very similar inspectional observations. Briefly, each of these sites was found to have adequately conducted the protocol, and in all cases the primary efficacy endpoint data were verifiable against source records at each site audited. However, there were multiple instances where protocol-specified assessments were not done at certain visits. DSI reviewer Lauren Iacono-Connors presented and discussed these inspectional findings with the review division (DBOP) Medical Officer, Dr. Martha Donoghue. The DSI reviewer and DBOP MO agreed that while "overall sloppiness" is disturbing from a protocol compliance standpoint, that the missed assessments are unlikely to significantly impact safety or primary efficacy analyses. However, the review division may wish to consider the impact of these inspectional observations on other study analyses, including secondary efficacy endpoints.

The inspection of the sponsor, Eisai, and CRO, (b) (4), resulted in parallel inspectional observations related to problematic monitoring activities and oversight of monitoring. The CRO was responsible (under contractual agreement) for all monitoring, data collection, and statistical analyses. However, selection of monitors remained with the sponsor. The sponsor and CRO inspections were primarily focused on monitoring activities and the qualifications of the monitors. The FDA field investigator noted that site monitoring, specifically, monitoring during most of the active enrollment/treatment phase, failed to meet the terms of the contract agreement with the sponsor. According to the [agreement] sites were to be visited within two weeks of the first subject enrollment at that site. Additionally, monitoring reports were to be provided to the sponsor within 15 days of a monitoring visit. According the FDA field investigator the Sponsor and the CRO identified this monitoring deficiency while the study was ongoing. They met and agreed to bring on more CRAs but the CRO was unable to find additional CRAs meeting the experience requirements outlined in the monitoring plan in a timely manner. By late 2008, the CRO was able to "get caught up" with the backlog of monitoring reports. The FDA field investigator reported that current monitoring and reporting appear to be in compliance with the monitoring plan.

While monitoring activities failed to meet the terms of the agreement between the CRO and the Sponsor, and the conditions outlined in the protocol, monitoring reports indicate that oversight of all reviewed sites was adequate. The FDA field investigator reported that they found no evidence to suggest a lack of reliability of efficacy data or significant underreporting of safety data.

The review division may, wish to consider each inspectional observation outlined in each of the Form FDA 483s, as described above, and sensor subject-specific or site-specific data from study analyses as appropriate. However, although regulatory violations were noted as described above, these are unlikely to significantly impact data reliability. The final reports (EIRs) for these inspections have not been completed to date.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the outstanding EIRs and supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

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

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/s/

LAUREN C IACONO-CONNORS
09/02/2010

TEJASHRI S PUROHIT-SHETH
09/02/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 2, 2010
To:	Patricia Keegan, MD, Director **Division of Biologic Oncology Products**
Through:	Mary Willy, PhD, Deputy Director **Division of Risk Management (DRISK)** Sharon R. Mills, BSN, RN, CCRP Patient Product Information Reviewer, Acting Team Leader **Division of Risk Management**
From:	Robin Duer, MBA, BSN, RN Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Halaven (eribulin mesylate Injection)
NDA #	201532
Applicant/sponsor:	Eisai, Inc.
OSE RCM #:	2010-762

1. INTRODUCTION

This review is written in response to a request by the Division of Biologic Oncology Products (DBOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for Halaven (eribulin mesylate Injection).

On March 30, 2010, Eisai, Inc. submitted a new drug application, NDA 201-532 for Halaven (eribulin mesylate Injection). Halaven is a microtubule inhibitor indicated 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. Eisai requested and DBOP granted priority review status for this application.

We plan to attend the meeting that DBOP has already scheduled for August 17, 2010 to discuss this review.

2. MATERIAL REVIEWED

- Draft Halaven (eribulin mesylate Injection) Prescribing Information (PI) submitted March 30, 2010, revised by the Review Division throughout the current review cycle and submitted to DRISK on July 21, 2010.

- Draft Halaven (eribulin mesylate Injection) Patient Package Insert (PPI) submitted on March 30, 2010, revised by the Review Division throughout the current review cycle and submitted to DRISK on July 20, 2010.

3. RESULTS OF REVIEW

In our review of the PPI, we have:

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

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

Please let us know if you have any questions.

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

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

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/s/

MELISSA I HULETT
08/02/2010

MARY E WILLY
08/02/2010
I concur

**Division of Drug Marketing,
Advertising, and Communications**

Internal Consult

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

To: Vaishali Jarral, Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D.
Division of Drug Marketing, Advertising and Communications, CDER

Date: August 2, 2010

Re: **Halaven (eribulin mesylate) injection**
NDA 0201532
Comments on draft product labeling

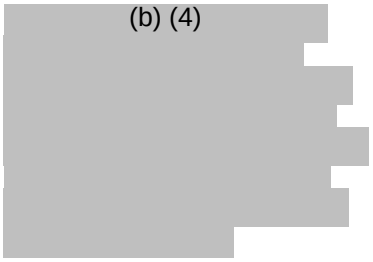
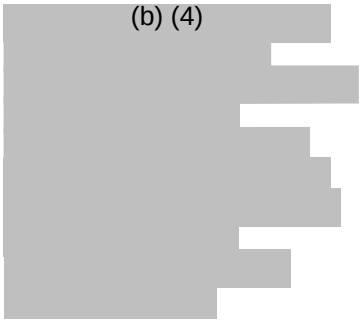
In response to DBOP's Request for Consultation dated April 7, 2010, DDMAC has reviewed the draft product labeling (PI) for Halaven. The version of the draft PI used in this review was sent via email from DBOP on July 20, 2010.

Proposed indication: Treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane.

Halaven is in a new "Halichondrin" class of antineoplastic agent.

DDMAC offers the following comments.

Section	Statement from Draft	Comment
HIGHLIGHTS & FULL PRESCRIBING INFORMATION INDICATIONS AND USAGE	**HIGHLIGHTS** (b) (4)	The indication should not allow broadening of the patient population and should reflect what was studied. The current indication statement broadens the patient population compared to the information contained in the Clinical Studies section. The Clinical Studies section

	FULL PRESCRIBING INFORMATION (b) (4) 	limits the patient population to patients that also "experienced disease progression within 6 months of their last chemotherapeutic regimen." DDMAC recommends including this limitation to the patient population to the Indications and Usage statement.
HIGHLIGHTS DOSAGE AND ADMINISTRATION **FULL PRESCRIBING INFORMATION** WARNINGS AND PRECAUTONS 5.1 Neutropenia	**HIGHLIGHTS** (b) (4)  **FULL PRESCRIBING INFORMATION** (b) (4) 	Other Full Prescribing Information (FPI) sections (2.1 and 8.6) of the PI define "mild" and "moderate" hepatic impairment as "Child's Pugh A" and "Child's Pugh B," respectively. DDMAC recommends defining "**mild** and **moderate** hepatic impairment" in the Highlights – Dosage and Administration section and the FPI section 5.1 (Neutropenia) the same as in FPI sections 2.1 (Recommended Dose) and 8.6 (Hepatic Impairment) using the Child's Pugh criteria. Is there a Child's Pugh criteria for "severe" hepatic impairment? If so, DDMAC recommends defining "severe" hepatic impairment using the Child's Pugh criteria.
FULL PRESCRIBING INFORMATION: CONTENTS and FULL PRESCRIBING INFORMATION		Please ensure that the numbering and sections in the **FULL PRESCRIBING INFORMATION: CONTENTS** correspond to the numbering and sections in the **FULL PRESCRIBING INFORMATION.** For example, the **FULL PRESCRIBING INFORMATION: CONTENTS** contains section 2.3 Dose Modification in Special Populations – Hepatic Impairment; however, the **FULL PRESCRIBING INFORMATION** does not

		contain a section 2.3. Also, the **FULL PRESCRIBING INFORMATION: CONTENTS** shows section 8.2 for Nursing Mothers; however, the **FULL PRESCRIBING INFORMATION** shows section 8.3 for Nursing Mothers.
FULL PRESCRIBING INFORMATION WARNINGS AND PRECAUTONS 5.1 Neutropenia	(b) (4)	Section "8.5" refers to the *Use in Specific Population – Geriatric Use* section of the PI. DDMAC recommends changing "8.5" to "8.6". Section "8.6" refers to the *Use in Specific Population – Hepatic Impairment* section of the PI.
FULL PRESCRIBING INFORMATION DRUG INTERACTIONS 7.1 Effects of Other Drugs on Halaven	(b) (4) [emphasis added]	The word (b) (4) " is promotional in tone and inappropriate for labeling. DDMAC recommends deletion of the word "(b) (4)."
FULL PRESCRIBING INFORMATION USE IN SPECIFIC POPULATIONS 8.6 Hepatic Impairment	(b) (4) [emphasis added]	Is there a Child's Pugh criteria for "severe" hepatic impairment? If so, DDMAC recommends defining "severe" hepatic impairment using the Child's Pugh criteria.
FULL PRESCRIBING INFORMATION USE IN SPECIFIC POPULATIONS 8.7 Renal Impairment	(b) (4)	"Mild," "moderate," and "severe" are appropriate terms to define renal impairment only if the cutoffs are clearly defined. DDMAC recommends defining the cutoffs for "mild," moderate," and "severe" renal impairment.

	[emphasis added]	
FULL PRESCRIBING INFORMATION CLINICAL PHARMACOLOGY 12.1 Mechanism of Action	Halaven exerts its (b) (4) effects via a tubulin-based antimitotic mechanism leading to G_2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage. [emphasis added]	The words (b) (4) " is promotional in tone and broadens the indication for Halaven. ' (b) (4) implies that Halaven is indicated (b) (4) in addition to breast cancer. DDMAC recommends deletion of the word (b) (4)
FULL PRESCRIBING INFORMATION CLINICAL PHARMACOLOGY 12.3 Pharmacokinetics - Distribution	(b) (4) [emphasis added]	The words (b) (4) and (b) (4) " are promotional in tone. DDMAC recommends deleting these words and instead provide the actual length of time.

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

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/s/

CAROLE C BROADNAX
08/02/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

******PRE-DECISIONAL AGENCY INFORMATION******

Date: August 2, 2010

To: Vaishali Jarral, Regulatory Project Manager
Division of Biologic Oncology Products (DBOP)

From: Cynthia Collins, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Cc: Shefali Doshi, Group Leader (DDMAC)
Carole Broadnax, Regulatory Review Officer (DDMAC)

Re: **NDA 201532**
Halaven (eribulin mesylate injection)
DDMAC consult response, Halaven PPI

DDMAC has reviewed the following draft patient labeling for Halaven:

- Draft Patient Prescribing Information (PPI)
  - document entitled "nda201532-PATIENT INFORMATION LEAFLET-OSE_DDMAC"
  - revised July 21, 2010
  - accessed from July 21, 2010, e-mail from Vaishali Jarral

DDMAC has provided comments on the Prescribing Information for Halaven under separate cover. Please see the attached pages for DDMAC's comments regarding the Halaven PPI.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions regarding the consumer directed materials for Halaven, please contact:

- Cynthia Collins
  (301) 796-4284
  e-mail: cynthia.collins@fda.hhs.gov

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

This Patient Package Insert has been approved by the U.S. Food and Drug Administration

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

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/s/

CYNTHIA S COLLINS
08/02/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: July 14, 2010 **Date Consulted:** April 14, 2010

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff (PMHS)

Through: Karen B. Feibus, M.D.
Medical Team Leader, Maternal Health Team (MHT)

Lisa Mathis, MD
OND Associate Director, Pediatric and Maternal Health Staff (PMHS)

To: Division of Biologic Oncology Products (DBOP)

Drug: Eribuin Mesylate Injection, NDA 201532

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed:

- Sponsor NDA submission dated March 30, 2010
- Draft Eribulin Mesylate Injection labeling dated March 30, 2010
- Draft DBOP Pharmacology/Toxicology Review of Reprotoxicity Studies

Consult Question: DBOP requests that MHT review and comment on the proposed Pregnancy and Nursing Mothers labeling for eribulin mesylate injection.

INTRODUCTION

Eisai, Inc. submitted a New Drug Application (NDA) 201532, on March 30, 2010, 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 a taxane. Eisai, Inc. is currently seeking simultaneous approval of the drug in the U.S., the E.U., and Japan.

On April 14, 2010, the Division of Biologic Oncology Products (DBOP) consulted the Maternal Health Team (MHT) to review and comment on the proposed pregnancy and nursing mothers sections of labeling.

BACKGROUND

Eribulin Mesylate Injection

Eribulin mesylate is the mesylate salt of a synthetic analogue of halichondrin B, a substance derived from a marine sponge (Lissodendoryx sp.) with antineoplastic activity. Eribulin binds to the vinca domain of tubulin and inhibits the polymerization of tubulin and the assembly of microtubules, resulting in inhibition of mitotic spindle assembly, induction of cell cycle arrest at G2/M phase, and, potentially, tumor regression.[1]

Cytotoxic Drugs and Pregnancy Labeling

Cytotoxic drugs interfere with normal cell growth. Based on this well-understood mechanism of action, the MHT in conjunction with the Division of Drug Oncology Products (DDOP) classify all current cytotoxic drugs as pregnancy category D.

FDA currently classifies the reproductive and developmental risk of drugs for use during pregnancy into five categories (A, B, C, D, and X)[2] using animal and human data (if available). Some of the categories consider the potential risk of the drug versus the potential benefit to a woman if used during pregnancy. Given the consideration of relative risk and benefit for a specific drug when used during pregnancy, the classification system does not represent a linear increase in risk for pregnancy category A to pregnancy category X (see Appendix A for a description of each pregnancy category). The MHT notes that the pregnancy category classification will be eliminated when the Final Pregnancy and Lactation Labeling Rule (PLLR) publishes (Proposed Pregnancy and Lactation Labeling Rule published May 29, 2008).[3] When the final regulations publish, the PLLR will complete the requirements on content and format of labeling for human prescription drug and biological products (Physician Labeling Rule, January 24, 2006, 71 FR 3922) by revising the content and format requirements for the pregnancy, labor and delivery, and nursing mothers subsections of labeling. The proposed changes to prescription drug labeling will provide prescribers with clinically relevant and more comprehensive information for making prescribing decisions and for counseling women who are pregnant, human milk-feeding, or of childbearing age about using prescription medications.

In addition, the PLLR, when it publishes, will recognize the importance of a well understood drug mechanism of action and will require the pregnancy risk summary to state when a well-

[1] See http://www.cancer.gov/drugdictionary/?CdrID=257773
[2] See Appendix A for pregnancy category definitions table
[3] See Proposed Pregnancy and Lactation Labeling Rule, 73 FR 30831, May 29, 2008

understood mechanism of action raises concerns about potential drug-associated adverse developmental effects.

Pregnancy and Nursing Mothers Labeling
Until the PLLR publishes, the Maternal Health Team has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations, including the assignment of pregnancy categories, but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes describing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount, as this can vary significantly from species to species.

This review provides MHT's suggested revisions to the proposed pregnancy and nursing mothers labeling for eribulin mesylate injection.

REVIEW OF PROPOSED LABELING (dated March 30, 2010)

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

(b) (4)

DISCUSSION AND CONCLUSIONS

Eribulin mesylate is cytotoxic and, therefore, based on its mechanism of action as a microtubule inhibitor, can cause embryofetal harm in humans. In addition, embryofetal toxicity and teratogenicity occurred in studies with animals that received eribulin mesylate at dose exposures lower than the recommended human dose based on body surface area calculations. This information should be adequately conveyed in Pregnancy subsection as well as in the WARNINGS section of labeling. The Pregnancy subsection should only include information about use in pregnancy. Information regarding use in women of childbearing potential (i.e., pregnancy avoidance and contraceptive use) should be placed as a separate warning in WARNINGS AND PRECAUTIONS and in the PATIENT COUNSELING INFORMATION section of labeling.

The proposed Nursing Mothers subsection adequately conveys the concerns with human milk feeding and potential serious adverse effects in the human milk-fed infant. In addition, the American Academy of Pediatrics, Committee on Drugs, recommends against human milk feeding during maternal cytotoxic drug treatment as cytotoxic drugs may interfere with cellular metabolism in a human milk-fed child.[4]

The MHT is structuring the Pregnancy and Nursing Mothers label information in a way that complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

[4] American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human milk. PEDIATRICS Vol. 108 No. 3 September 2001

MHT's recommended labeling revisions for eribulin mesylate labeling are provided below. Appendix B of this review also provides a track changes version of labeling.

MHT LABELING RECOMMENDATIONS
MHT Labeling Recommendations (from DBOP labeling meeting, July 13, 2010)

HIGHLIGHTS OF PRESCRIBING INFORMATION

--————————WARNINGS AND PRECAUTIONS————————

- Fetal harm is expected to occur when administered to a pregnant woman (5.2, 8.1).
- Women of Childbearing Potential: Avoid pregnancy and use effective contraception (5.3).

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Discontinue drug or nursing taking into consideration the importance of drug to the mother. (8.3)

5 WARNINGS
5.2 Pregnancy
There are no adequate and well-controlled studies with Halavan in pregnant women. Halavan is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryofetal toxicity and teratogenicity occurred in animals that received Halavan at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*

5.3 Women of Childbearing Potential
Advise women of childbearing potential to avoid becoming pregnant and to use effective contraception during treatment with TRADENAME. *[see Use in Specific Populations (8.1)]*.

Reviewer Comment:
Women of childbearing potential are not pregnant; therefore, specific information regarding this group should be placed in subsections separate from use in pregnancy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.3)]
There are no adequate and well-controlled studies with Halavan in pregnant women. Halavan is a microtubule inhibitor; therefore, it is expected to cause fetal harm when administered to a pregnant woman. Embryofetal toxicity and teratogenicity occurred in animals that received Halavan at approximately half of the recommended human dose based on body surface area. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

In a developmental toxicity study, pregnant rats received intravenous infusion eribulin mesylate during organogenesis (Gestation Days 8, 10, and 12) at doses approximately 0.04, 0.12, 0.42 and 0.64 times the recommended human dose based on body surface area (mg/m^2). External or soft tissue anomalies were observed at doses 0.64 times the recommended human dose based on body surface area (mg/m^2). Eribulin mesylate caused increased abortion and severe malformations in the offspring, including the absence of a lower jaw, absence of a tongue, absence of stomach and absence of spleen. Increased embryo fetal death/resorption, reduced fetal weights and minor skeletal anomalies consistent with developmental delay were also reported at doses at and above 0.42 times the recommended human dose.

Maternal toxicity of eribulin mesylate was reported in rats at doses of 0.42 times the recommended human dose (mg/m^2) and above, and included enlarged spleen, reduced maternal weight gain and decreased food consumption.

8.3 Nursing Mothers

It is not known whether Halavan is excreted into human milk. No studies in humans or animals were conducted to determine if Halaven is excreted into milk. Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in human milk-fed infants from Halavan, a decision should be made whether to discontinue nursing or to discontinue Halavan taking into account the importance of the drug to the mother.

Reviewer Comment:

We searched the Drugs and Lactation database (LactMed)[5] and found no human lactation data for eribulin mesylate.

17 PATIENT COUNSELING INFORMATION

17.2 Women of Childbearing Potential

Advise women of childbearing potential to avoid pregnancy and to use effective contraception during treatment with Halavan *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

[5] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT

APPENDIX A:
FDA Pregnancy Category Definitions

Table 1. FDA Pregnancy categories
(language summarized from 21 CFR 201.57)

Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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APPENDIX B – MHT Tracked-Changes Labeling Revisions

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/s/

JEANINE A BEST
07/14/2010

Karen B FEIBUS
07/14/2010
I agree with the content and recommendations contained in this review.

LISA L MATHIS
07/20/2010

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	201532
Generic Name	Eribulin mesylate
Sponsor	Eisai, Inc.
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.
Dosage Form	Intravenous injection
Drug Class	Antineoplastic agent-microtubule dynamics inhibitor
Therapeutic Dosing Regimen	1.4 mg/m^2
Duration of Therapeutic Use	Chronic (till disease progression or DLT)
Maximum Tolerated Dose	(b) (4)
Submission Number and Date	SDN 001, March 30, 2010
Review Division	DDOP/DBOP/HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

A delayed QTc interval prolongation was observed in the dedicated QT study. The largest upper bound of the 2-sided 90% confidence interval (CI) for the change from baseline in QTcF was 18 ms observed on Day 8. In this open-label, uncontrolled, multicenter, single-arm dedicated QT study, patients with advanced solid tumors received 1.4 mg/m^2 of eribulin mesylate on days 1 and 8 of a 21- day cycle. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the Two-sided 90% CIs Corresponding to the Largest Upper Bounds for Eribulin Mesylate (1.4mg/m^2) (FDA Analysis)

Treatment	Day	Time (hour)	ΔQTcF (ms)	90% CI (ms)
Eribulin Mesylate 1.4 mg/m^2	8	0.25	11.3	(4.4, 18.2)

A supratherapeutic dose was not evaluated in the dedicated QT study. A 1.5-fold increase in C_{max} was observed in patients with moderate hepatic impairment (worst case scenario) compared with normal subjects. However, the current QT study demonstrated no apparent concentration-QT relationship, suggesting that the increase in exposure is not directly associated with QTc interval change. In addition, the sponsor proposed a dose reduction by half (0.7 mg/m^2) for patients with moderate hepatic impairment.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- Given the delayed effect on the QTc interval observed in this study, we recommend that the sponsor explores this with further non-clinical testing by
    - performing a hERG trafficking study for parent and relevant metabolites with concurrent positive control like arsenic trioxide and pentamidine.
    - performing a study to detect delay in distribution to myocardium.

2 LABEL

2.1 SPONSORS PROPSED LABEL

(b) (4)

2.2 QT-IRT RECOMMENDATION

QT-IRT recommendations for labeling are suggestions only; we defer final decisions related to labeling to the review division.

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Eribulin mesylate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. The proposed indication is for the treatment of patients with (b) (4) or metastatic breast cancer previously treated with at least two chemotherapeutic regimens. The proposed dose is 1.4 mg/m^2 (as the mesylate salt) administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

3.2 MARKET APPROVAL STATUS

Eribulin is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Source Non-clinical summary, eCTD 2.6.2

> "Effects on HERG Tail Currents Recorded from Stably Transfected HEK293 Cells (Study No. SPH03-001)
>
> "This in vitro study examined the effects of eribulin mesylate on hERG tail current recorded from human embryonic kidney 293 (HEK293) cells stably transfected with hERG complementary DNA (cDNA).
>
> "Exposure to 0.1% ethanol (vehicle) for approximately 15 minutes resulted in a mean decrease in tail current of 16.4% (n = 4 cells/group). Exposure to 30 µmol/L eribulin mesylate for approximately 15 minutes resulted in a mean decrease in tail current of 23.2% (n = 4 cells). Because no significant difference between the vehicle-treated and 30 µmol/L eribulin mesylate treated groups was observed, the effects of lower concentrations of eribulin mesylate were not investigated. When 100 nmol/L of the reference substance E-4031 (positive control) was applied to four cells (two previously exposed to vehicle and two previously exposed to eribulin mesylate) for approximately 10 to 15 minutes, hERG tail current was inhibited by 74.6% (meandecrease from all four cells).
>
> "Thus treatment with 30 µmol/L eribulin mesylate produced no inhibition of hERG tail current in HEK293 cells stably transfected with hERG cDNA.
>
> "2.6.2.4.2 Effects on Action Potential Parameters in Isolated Cardiac Purkinje Fibers of Dog (Study No. SPP03-002)
>
> "This in vitro study examined the effects of perfusion of eribulin mesylate at concentrations of 1, 10 and 30 µmol/L on intracellularly recorded action potential parameters in the isolated dog Purkinje fiber preparations. In isolated dog Purkinje fibers (n = 4 specimens/group), paced at a stimulation frequency of 1 Hz, resting membrane potential (RMP), upstroke amplitude (UA), maximum rate of depolarization (MRD) and action potential duration at 60% and 90% repolarization (APD60 and APD90) were determined. The effects of increasing concentrations of eribulin mesylate (1, 10 or 30 µmol/L, 30 minutes at each concentration), or 0.1% ethanol (vehicle) for these same parameters were

evaluated at stimulation frequencies of 1 Hz followed by 0.5 Hz (four fibers for eribulin mesylate and four fibers for vehicle). Eribulin mesylate had no effect on RMP, UA, MRD, APD60 or APD90 at either the 1 Hz or the 0.5 Hz stimulation frequencies. The effects of 30 μmol/L of eribulin mesylate on changes in MRD at a stimulation frequency of 1 and 3 Hz were compared to the MRD for 0.5% ethanol and there was no significant difference between the two groups.

"In conclusion, eribulin mesylate at concentrations of 1, 10 and 30 μmol/L showed no effect on evoked action potentials in isolated dog Purkinje fibers.

"2.6.2.4.3 Effects on Cardiovascular System and Body Temperature by Intravenous Infusion in Conscious Dogs (Study No. SPT03-001)

Intravenous infusion of eribulin mesylate at 0.01 mg/kg had no biologically meaningful effects on the cardiovascular system or on core body temperature in male and female dogs. Eribulin mesylate, when infused at 0.04 mg/kg, was associated with transient decreases in SBP, DBP, MAP and HR and an increased RR interval in male and female dogs. There were no significant effects on the other lead II ECG parameters nor on core body temperature."

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety eCTD 2.7.4

Pooled safety data is available from 1222 eribulin-treated subjects from 11 Phase 1, 2 and 3 completed studies. A total of 827 breast cancer subjects receiving eribulin according to the proposed dose regimen in three completed studies, two Phase 2 studies (Studies 211 and 201) with a data cut-off of 31 May 2009) and one Phase 3 study. The subjects had received prior chemotherapy (including anthracyclines). Subjects with significant cardiovascular impairment (history of congestive heart failure > New York Heart Association [NYHA] Class II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia) were excluded from the studies.

The sponsor reported that in the All Eribulin Treated population, cardiac system organ class (SOC) disorders occurred in 108 (8.8%) and 63 (7.6%) subjects in the All Eribulin Treated and Breast Cancer Populations, respectively (Integrated Safety Data, Table 2.1.2). Cardiac treatment-emergent adverse events (TEAEs) reported with the highest incidence were tachycardia (49 [4.0%] and 30 [3.6%] subjects, respectively), and palpitations (23 [1.9%] and 15 [1.8%] subjects, respectively). There were 2 cases of arrhythmia, 2 cases of first degree heart block, and 1 case each of atrial fibrillation and supraventricular tachycardia (Integrated Safety Data, Table 2.1.4). There were no events of torsade de pointes in this group of subjects treated with eribulin. In Study 211, Subject 04280705 died as a result of a serious TEAE of cardiac arrest with onset at Cycle 2, Day 62 and was considered not related to study drug, since the event occurred over 30 days after the last dose of eribulin was administered. Subject 04680502 died due to "unknown reason", five days after receiving eribulin (Cycle 2 Day 1), which could potentially have been due to a cardiac event, and was considered as possibly related by the investigator.

In the phase 3 study, the incidence of cardiac SOC TEAEs was slightly higher for eribulin (33 [6.6%] subjects) than treatment of physician's choice (TPC), (10 [4.0%]

subjects The sponsor re-analyzed cardiac AEs by time of exposure and reports that the rates of cardiac disorder SOC TEAEs per 100 subject days were similar between eribulin and TPC treated subjects (33 [0.05%] and 10 [0.04%], respectively.

In 2 of the studies (201 and 202) ECGs were recorded immediately pre-dose and at the anticipated peak plasma concentration (C_{max}) of the drug and ECGs were centrally read. The total number of patients with ECGs recorded both immediately pre-dose and at C_{max} in any of the studies was relatively small; 118 (18 in Study 201 and 100 in Cycle 1 in Study 202). In both studies, the dose of E7389 was 1.4 mg/m^2 over 1 to 5 minutes as a once weekly infusion for 2 or 3 weeks in 21- or 28-day cycles. Small effects on QTcF were noted (see below). There were no QTcF values exceeding 500 ms at baseline or after dosing of E7389

Table 5: ECG parameters, Study E7389-A002-201

	Predose Day 1, Cycle 1		Post-dose Day 1, Cycle 1		Change	
	N	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
RR, ms	27	741 (149)	18	792 (129)	18	61 (78)
PR, ms	27	148 (21)	18	152 (23)	18	4 (10)
QRS, ms	27	84 (10)	18	86 (10)	18	0 (12)
QT, ms	27	358 (37)	18	372 (30)	18	12 (11)
QTcF, ms	27	397 (25)	18	403 (22)	18	3 (13)

Table 10: QTcF interval, Study E7389-A001-202

			Δ Baseline*	90% CI for Δ Baseline**
Baseline	*N*	103		
	Mean (SD) ms	403 (21.2)		
Cycle 1 Day 1 pre-dose	*N*	103		
	Mean (SD) ms	404 (23.8)		
Cycle 1 Day 1 post-dose	*N*	100	100	
	Mean (SD) ms	406 (23)	2.5 (13.8)	-20 to 25
Cycle 3 Day 1 pre-dose	*N*	52	52	
	Mean (SD) ms	414 (21.2)	8.4 (17)	-20 to 36
Cycle 3 Day 1 post-dose	*N*	51	51	
	Mean (SD) ms	417 (22.2)	11.4 (20)	-22 to 44
Cycle 5 Day 1 pre-dose	*N*	29	29	
	Mean (SD) ms	412 (16.6)	4.6 (12.8)	-16 to 26
Cycle 5 Day 1 post-dose	*N*	30	30	
	Mean (SD) ms	413 (20.2)	5.8 (16.2)	-21 to 32
Cycle 7 Day 1 pre-dose	*N*	20	20	
	Mean (SD) ms	414 (24.6)	2.5 (16.2)	-24 to 29
Cycle 7 Day 1 post-dose	*N*	19	19	
	Mean (SD) ms	418 (21)	5.1 (12)	-15 to 25

(Source: ECG Review of E7389 Program, March 22, 2009 by Dr. Borje Darpo)

In study 305, a standard 12-lead ECG was taken for all subjects at Screening and at Study Termination. In addition, subjects randomized to eribulin mesylate treatment had an on-treatment ECG prior to starting Cycle 2. It was recommended this ECG was scheduled for Day 1 of Cycle 2 prior to eribulin mesylate dosing. ECGs were complete, standardized 12-lead recordings. Four subjects (0.8%) treated with eribulin had abnormal clinically significant ECGs at study termination. Grade 2 or 3 QT prolongation were reported as AEs but a categorical analysis of QT was not available in the CSR.

- Patient 23021005 (eribulin) with ST depression at the anterior leads. The patient had cardiac AEs of hypertension and atrial tachycardia.
- Patient 28151010 (eribulin) with probable left ventricular hypertrophy. The patient had no cardiac AEs reported.
- Patient 28151015 (eribulin) with diffuse low voltage. The patient had no cardiac AEs reported.
- Patient 14021003 (TPC- gemcitabine) with cardiac insufficiency. Cardiac failure was reported as an AE.
- Patient 19061011 (TPC- capecitabine) with ventricular premature beats. No AEs were reported for this patient

Reviewer's Comments: There are no reports of significant ventricular arrhythmias or TdP. No definitive conclusions can be made about the case of sudden death with cause

unknown since ECG data are unavailable and there is confounding due to co-morbidities.
Delayed effects on QTcF (although small) are also noted in study 202.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of eribulin mesylate's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 67913. The sponsor submitted the study report E7389-E044-110 for the study drug, including electronic datasets. Waveforms to the ECG warehouse were also submitted.

4.2 QT STUDY

4.2.1 Title

An Open-Label, Multicenter, Single Arm QT Interval Prolongation Study of Eribulin Mesylate (E7389) in Patients with Advanced Solid Tumors

4.2.2 Protocol Number

E7389-E044-110

4.2.3 Study Dates

February 24, 2009- July 22, 2009

4.2.4 Objectives

PRIMARY:

To assess whether eribulin mesylate has an impact on the ECG with focus on cardiac repolarization, as measured by QT/QTc interval as well as through a pharmacokinetic-pharmacodynamic (PK/PD) analysis.

SECONDARY :

- To further characterize the pharmacokinetic profile of eribulin mesylate.
- To assess best overall response using Response Evaluation Criteria In Solid Tumors (RECIST) criteria in patients with measurable disease.
- To further explore the safety and tolerability of eribulin mesylate when administered on Days 1 and 8 of a 21-day cycle in patients with solid tumors

4.2.5 Study Description

This was an uncontrolled, open-label, multicenter, single-arm Phase 1 study to determine the effect of eribulin mesylate on cardiac repolarization in patients with histologically or cytologically confirmed advanced solid tumors that had progressed following standard therapy or for which no standard therapy existed (including surgery or radiation therapy).

4.2.6 Treatment Regimen

Treatment with eribulin mesylate (1.4 mg/m2 IV infusion given over 2-5 minutes) was administered in the morning on Days 1 and 8 of a 21-day Study phase (Cycle 1).

4.2.6.1 Sponsor's Justification for Doses

> "In the Phase 1 studies the MTD was determined to be 1.4 mg/m^2 when administered as a bolus on Days 1, 8, and 15 of a 28-day cycle. In two subsequent Phase 2 studies, in heavily pretreated patients with breast cancer and NSCLC, the Day 15 dose in the 28-day cycle had to be omitted in >50% of cases due to hematological toxicity. Efficacy, however, was not affected by skipping the Day 15 dose. It was concluded that 1.4 mg/m^2 (administered as an intravenous bolus on Days 1 and 8 of each 21 day cycle) was likely to be the optimal dose and schedule, and it is currently being investigated in Phase 2 and 3 studies with eribulin mesylate)."

(Source: Sponsor's Report, Section 9.4.4)

Reviewer's Comment: The sponsor's study design utilized a single-dose of 1.4 mg/m^2 administered as an IV bolus over 2-5 minutes. Since the clinically recommended dose for eribulin mesylate is 1.4 mg/m^2 (IV bolus), the sponsor's choice of the therapeutic dose seems reasonable. The sponsor did not evaluate a supra-therapeutic dose in their QT study. The maximum tested dose in their Phase 1 study were 4.0 mg/m^2 as a one-hour IV infusion on Days 1, 8 and 15 of a 28-day cycle and 2.0 mg/m^2 as a 5 minute IV infusion. A 1.4-fold increase in C_{max} was observed for the 2.0 mg/m^2 compared to the 1.4 mg/m^2 dose. Similar C_{max} was obtained for the 4.0-mg/m^2 (1 hour IV infusion) dose compared to the therapeutic dose. There is no significant accumulation of the drug upon multiple dose administration. A 1.2-fold and 1.5-fold increase in C_{max} was observed in patients with mild and moderate hepatic impairment compared with normal subjects. A dedicated renal study was not performed. However, no effect of mild and moderate renal impairment was observed on the clearance of the drug based on population PK analysis. Since <10% of the drug is excreted renally, the effect of renal impairment on drug PK is not anticipated. There was no effect of CYP3A4 inhibitor (ketoconazole) on the C_{max} of eribulin mesylate. Data are currently unavailable from an ongoing study to evaluate the effect of a CYP3A4 inducer (rifampicin) on the PK of eribulin mesylate. However, based on the in vitro results, population PK analysis and the elimination pathway of the drug significant effects are not anticipated.

4.2.6.2 Instructions with Regard to Meals

Patients were encouraged to eat the same or similar food at the same time on all days that the Holter ECGs were conducted.

(Source: Sponsor's Report, Table 3 page 49)

Reviewer's Comment: This is a product for intravenous injection; therefore, food effects are not anticipated.

4.2.6.3 ECG and PK Assessments

ECG Assessment

Triplicate 12-lead ECGs extracted from the continuous Holter were collected on Cycle 1, Day 0. The extractions were based on hypothetical time-matched start and end times of infusion (for predose and end of infusion time points). ECG was collected prior to start of infusion and at the end of infusion on Days 1 and 8 of Cycle 1. ECG's were extracted at 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 10, 24 and 48 hours after the start of drug administration on Days 1 and 8 of Cycle 1. ECG samples were collected just prior to PK blood sample collection.

(Source: Sponsor's Report, Section 9.5.3)

PK Assessment

Blood samples were collected for measurement of eribulin mesylate concentrations at 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 10, 24 and 48 hours after the start of drug administration on Days 1 and 8 of Cycle 1. Predose sample was collected immediately before drug administration.

(Source: Sponsor's Report, Section 9.5.4)

Reviewer's Comment: ECG measurements were collected frequently enough to monitor the effects of eribulin mesylate over a 24-hour interval. Frequent samples were collected around T_{max} of the drug in order to detect changes in the QT interval at maximum drug concentrations.

4.2.7 ECG Collection

Patients wore the Holter recorder and the 12-Lead ECGs were captured continuously, according to the collection schedule outlined above. The core lab (eRT) analyzed ECGs using semi-automated, on-screen caliper method.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 31 patients with advanced cancer disease were screened for this study at 5 investigational centers. 26 patients were enrolled and received study treatment. Twenty-four patients completed the Study phase (Cycle 1). Two patients were discontinued from the study before completion of the study phase: Patient 1005-1002 was discontinued due to an SAE (Grade 3 renal failure) and study medication was withdrawn prior to the Cycle 1 Day 8 dose. Patient 1004-1002 was discontinued prior to receiving the Cycle 1 Day 8 dose due to progression of disease. Patient 1002-1007 did not receive study drug on Cycle 1 Day 8 due to AE of (Grade 4 neutropenia), but subsequently recovered from AE and resumed treatment at Cycle 2 Days 1 and 8.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

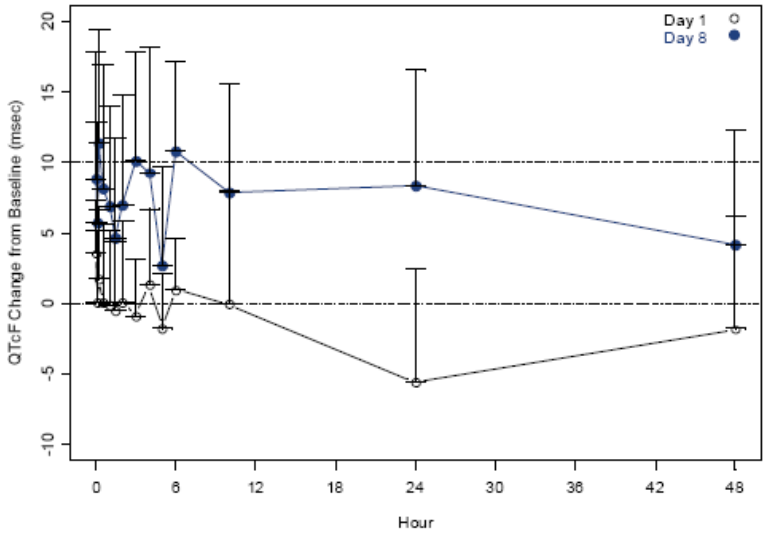
The primary end point of interest was the largest mean difference between the time-matched baseline QTcF to post-dosing QTcF, considering all post-treatment assessments on Day 1 and Day 8,
On Day 1, QTcF mean changes from the time matched baseline were close to zero, indicating no difference between Cycle 1 Day 1 and the time-matched baseline.
On Day 8, the changes from baseline were larger and the variability substantially higher, resulting in wider confidence intervals (Table 16 and Figure 1). Time-matched pre-dose QTcF on Day 8 was 9 ms and all post-dose QTcF intervals varied +/-3 ms around the pre-dose value, ranging from 6 to 11 ms. The largest mean baseline-adjusted QTcF post-dosing of eribulin was 11 (upper CI 19.5 ms) at 15 minutes post-dosing.

Table 2: Mean and One-side 95% CI of QTcF Change from Baseline vs Time Profile: Per Protocol Population

	Day 1			Day 8		
Time (hours)	N	Mean (SD) QTcF (msec)	Upper 95% CI	N	Mean (SD) QTcF msec	Upper 95% CI
0	23	4 (8.8)	7.3	20	9 (19.3)	17.9
0.08	26	0 (12.5)	5.1	22	6 (16.1)	12.9
0.25	26	2 (12.3)	6.7	23	11 (18.7)	19.5
0.5	26	0 (14.0)	5.7	23	8 (20.5)	17.0
1	26	0 (13.1)	5.1	23	7 (16.5)	14.0
1.5	25	-1 (12.0)	4.4	22	5 (16.1)	11.8
2	24	0 (13.6)	5.8	22	7 (17.5)	14.8
3	25	-1 (9.9)	3.2	23	10 (18.0)	17.9
4	24	1 (12.8)	6.7	22	9 (20.2)	18.2
5	26	-2 (9.6)	2.1	23	3 (16.3)	9.7
6	26	1 (9.1)	4.6	23	11 (14.7)	17.2
10	25	0 (19.6)	8.0	22	8 (17.3)	15.6
24	26	-6 (20.1)	2.5	23	8 (18.8)	16.5
48	26	-2 (20.0)	6.2	23	4 (19.1)	12.4

Source: Table 14.3.7.3

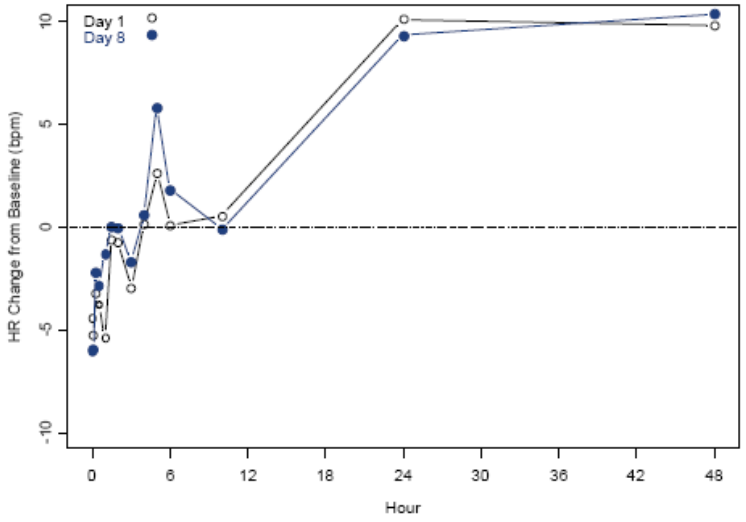
Figure 1: Mean and One-side 95% CI of QTcF Change from Baseline vs Time Profile: Per Protocol Population



Note: 24 and 48 hour ECGs are 12-lead ECGs.
Source: Table 14.3.7.3

For both Day 1 and Day 8 in Cycle 1, an initial reduction of the heart rate was observed during the first 1.5 hours after eribulin mesylate administration, which then returned to baseline levels.

Figure 2: Mean of Heart Rate Change from Baseline vs Time Profile: Per Protocol Population



Note: 24 and 48 hour ECGs are 12-lead ECGs.
Source: Table 14.3.7.2

4.2.8.2.2 Categorical Analysis

Cycle 1 Day 1 (including 24 and 48 hours)

There were no patients with QTcF interval durations of 470-500 ms or >500 ms during Day 1. A total of 5 patients had a change of >30 to 60 ms during the same period. None of the patients with a QTcF change of > 30-60 ms discontinued the study or had the eribulin mesylate dose reduced for the second infusion at Day 8 due to this change. No patients had a change in QTcF >60 ms at Cycle 1 Day 1.

Cycle 1 Day 8 (including 24 and 48 hrs)

During Day 8, one patient (Patient 1001-1001) had a QTcF 470-500 ms at several posteribulin mesylate infusion time points, and no patients had an QTcF interval value >500 ms.

Patient 1001-1001 (68 years, White male, with metastatic adenocarcinoma of the prostate [Stage IV, with pelvic and lumbar vertebral lesions]) had an abnormal elevated Day 8 predose Holter ECG., with a mean QTcF of 475 ms, and also an abnormal Day 1 pre-dose ECG (although QTcF was not elevated: 433 ms). Subsequent elevated mean QTcF measurements on Day 8 and corresponding time points were: 474 ms (15 min), 477 ms (1 hr), 473 ms (2 hours), 478 ms (3 hours), 496 ms (4 hours), 479 ms (5 hours), 470 ms (6 hours), and 495 ms (24 hours, 12-lead standard ECG measurement). Comments on the ECG measurements included: “flat, limb lead reversal”, “flat, precordial lead reversal” and “flat, prolonged QTc”. The 48-hours 12-lead standard ECG QTcF value had returned to normal (458 ms). The patient also had a mean change from baseline in QTcF of 65.33 ms at 4 hours post-eribulin mesylate infusion at Day 8.

A total of 10 patients had changes from baseline in QTcF of >30 to 60 ms post-infusion, which is twice the number of patients on Day 1. None of the patients discontinued the study. Patient 1001-1001 had a mean change from baseline in QTcF of 65.33 ms at 4 hours post-eribulin mesylate infusion at Day 8.

Table 3: Frequency of Categorical Changes from Baseline for Mean Time-Matched QTcF Interval Results: Per Protocol Population

			Change from Baseline in QTcF Number (%) of Patients		
ECG Parameter	Visit/Timepoint	N	0 - 30	30 – 60	>60
QTcF	Cycle 1 Day 1				
	15 mins	26	12 (46.2)	0	0
	30 mins	26	11 (42.3)	1 (3.8)	0
	1 hour	26	12 (46.2)	0	0
	1.5 hours	26	13 (50.0)	0	0
	2 hours	25	8 (32.0)	0	0
	3 hours	25	13 (52.0)	0	0
	4 hours	25	11 (44.0)	1 (4.0)	0
	5 hours	26	12 (46.2)	0	0
	6 hours	26	17 (65.4)	0	0
	10 hours	25	12 (48.0)	1 (4.0)	0
	24 hours	26	9 (34.6)	0	0
	48 hours	26	8 (30.8)	2 (7.7)	0
	Cycle 1, Day 8				
	15 mins	23	11 (47.8)	5 (21.7)	0
	30 mins	23	11 (47.8)	3 (13.0)	0
	1 hour	23	13 (56.5)	1 (4.3)	0
	1.5 hours	23	10 (43.5)	2 (8.7)	0
	2 hours	23	11 (47.8)	3 (13.0)	0
	3 hours	23	12 (52.2)	3 (13.0)	0
	4 hours	23	12 (52.2)	2 (8.7)	1 (4.3)
	5 hours	23	12 (52.2)	2 (8.7)	0
	6 hours	23	15 (65.2)	3 (13.0)	0
	10 hours	22	12 (54.5)	1 (4.5)	0
	24 hours	23	11 (47.8)	3 (13.0)	0
	48 hours	23	12 (52.2)	3 (13.0)	0

Percentage is based on total number of patients with non-missing test results at each visit.
Source: Table 14.3.7.6 and Listing 16.2.9.3.4

Table 4: Frequency Distribution of Abnormal Post-Baseline QTcF Values (Mean Time-Matched ECG Results): Per Protocol Population

		Number (%) of Patients		
ECG Parameter	Visit/Timepoint	Abnormal Values Newly Presented on Treatment[a]		
		N	470 – 500 msec	>500 msec
QTcF	Cycle 1 Day 1			
	15 mins	26	0	0
	30 mins	26	0	0
	1 hour	26	0	0
	1.5 hours	26	0	0
	2 hours	25	0	0
	3 hours	25	0	0
	4 hours	25	0	0
	5 hours	26	0	0
	6 hours	26	0	0
	10 hours	25	0	0
	24 hours	26	0	0
	48 hours	26	0	0
	Cycle 1, Day 8			
	15 mins	23	1 (4.3)	0
	30 mins	23	0	0
	1 hour	23	1 (4.3)	0
	1.5 hours	23	0	0
	2 hours	23	1 (4.3)	0
	3 hours	23	1 (4.3)	0
	4 hours	23	1 (4.3)	0
	5 hours	23	1 (4.3)	0
	6 hours	23	1 (4.3)	0
	10 hours	22	0	0
	24 hours	23	1 (4.3)	0
	48 hours	23	0	0

Percentage is based on total number of patients with non-missing test results at each visit.
Includes only patients for whom an abnormal value was first recorded at a given post-baseline visit.
Source: Table 14.3.7.5 and Listing 16.2.9.3.2 and 16.2.9.3.3

4.2.8.2.3 Additional Analyses

Changes from baseline to the last available data for Cycle 1 (Days 1 and 8) in 12-lead ECG Holter/digital results (PR, QRS, QT intervals and heart rate) from pre-dose (baseline) to the end of eribulin mesylate infusion, and 15 min, 30 min, 1, 1.5, 2, 3, 4, 5, 6, 10, 24 and 48 hours post-eribulin mesylate infusion, are summarized in Table 14.3.7.2 of the CSR. The sponsor reports no significant effects on the PR and QRS intervals.

4.2.8.3 Safety Analysis

There were no deaths during the study phase

7/26 patients experienced a total of 14 treatment-emergent SAEs. No patient experienced a cardiac-related SAE.

Patient 1005-1002 (aged 55 years, female) received 2.5 mg eribulin mesylate on Day 1 and study drug was withdrawn before the second infusion at Day 8 due to an SAE of renal failure on Study Day 6 (Grade 3, reported on Day 6, of 6 days' duration, considered probably related to study drug by the investigator;). This AE occurred in the context of severe neutropenia (Grade 4), and non-documented infection requiring antibiotic therapy and growth factor (G-CSF). The patient was reported as recovered at the point of data cut-off for this study. This patient also experienced an AE of presyncope on Study Day 6 (moderate severity, considered not related to study drug by the investigator, patient recovered).

Patient 1003-1002 experienced a non-serious AE of presyncope on Study Day 14 (an ECG was not done, Grade 2, not considered related to study drug by the investigator, patient recovered). This event occurred in the context of Grade 3 anorexia supplemented by enteral therapy (Kabiven), nausea and vomiting (Metochlopramide and metopimazine), and Grade 2 anemia (Hemoglobin level 9.9 g/dL).

Patient 1003-1004 experienced an AE of vertigo on Cycle 1 Day 3, in the context of Grade 1/2 sustained hypotension (from 12 to 24 June) requiring stoppage of antihypertensive therapy on 19 June. This patient had history of Grade 2 hypertension since 1999. The AE was Grade 1, not considered related to study drug by the investigator, and the patient recovered. An ECG was not done.

Patient 1004-1007 experienced an AE recorded as Grade 1 atrial fibrillation of brief duration (from 04 June to 05 June) on Cycle 1 Day 2. Cycle 1 Day 2 and Day 3 QTcF was 376 msec (-58 ms) and 428 ms (-6 ms), respectively, while QTcF time-matched baseline was 434 msec at both timepoints. The AE was not considered related to study drug by the investigator, and the patient recovered

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for eribulin mesylate are presented in Table 5. C_{max} and AUC values in the QT study were comparable on days 1 and 8 of cycle 1 following administration of the therapeutic dose (1.4 mg/m^2). The mean eribulin mesylate concentration profiles on days 1 and 8 of cycle 1 for the therapeutic dose are shown in Figure 3.

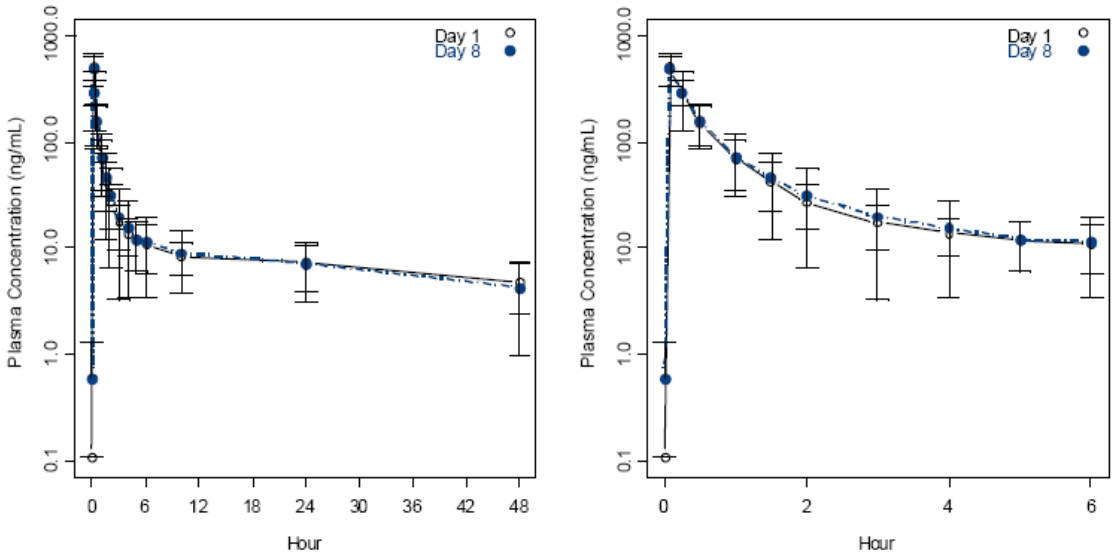
Table 5: Sponsor's Mean PK Parameters

Parameter	Cycle 1, Day 1 Mean (SD)	Cycle 1, Day 8 Mean (SD)
N	26	23
Actual data		
C_{max} (ng/mL)	516.5 (137.91)	502.4 (138.31)
t_{max} (hr)	0.08 (0.07 – 0.25)	0.08 (0.05 – 0.25)
$AUC_{(0\text{-}48\ hrs)}$ (ng.hr/mL)	628.1 (257.68)	629.1 (235.53)
Dose-normalized data		
C_{max} (ng/mL/mg)	239.6 (69.12)	234.3 (77.48)
$AUC_{(0\text{-}48\ hrs)}$ (ng.hr/mL/mg)	294.7 (133.54)	296.1 (138.86)

Data are shown as mean (SD), except for T_{max} which are median (range).

Source: Sponsor's Report, Table 21 page 96

Figure 3: Sponsor's Mean Eribulin Mesylate Concentration-time Profiles



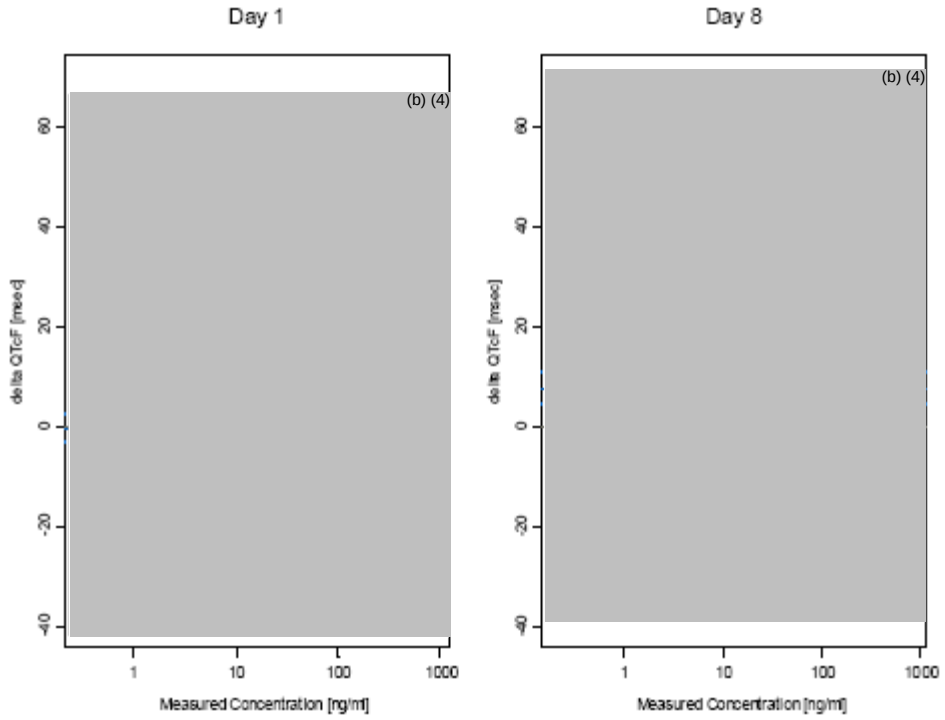
Data are shown as mean ± SD

Source: Sponsor's Report, Figure 3 page 95

4.2.8.4.2 Exposure-Response Analysis

Sponsor's ΔQTcF vs. eribulin mesylate plasma concentration plot for days 1 and 8 of cycle 1 are shown in Figure 4. Across the studied concentration range, there appeared to be no increase in QTcF duration. However, sponsor's linear mixed effect model shows an increase in the value of the intercept on day 8 compared to day 1.

Figure 4: Sponsor's ΔQTcF vs. Eribulin Mesylate Plasma Concentration



Source: Sponsor's Report, Figure 6, page 99

Reviewer's Analysis: Plots of ΔQTcF vs. eribulin mesylate concentrations on days 1 and 8 are presented in Figure 7. There appeared to be no increase in QTcF with increasing drug concentrations.

5 REVIEWERS' ASSESSMENT

5.1 CENTRAL TENDENCY ANALYSIS

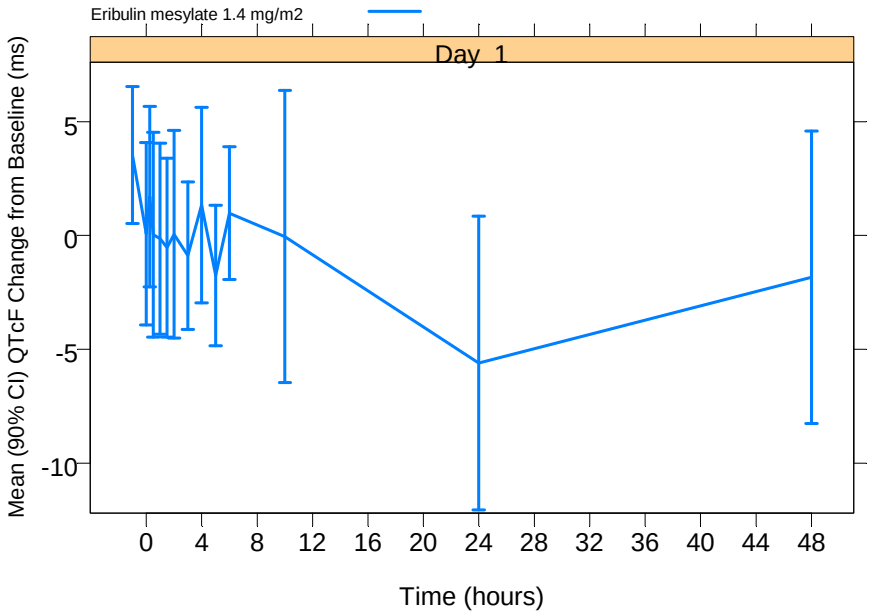
The mean and the 90% CI of baseline-adjusted QTcF (ΔQTcF) were calculated at each time point. The analysis results are presented in Table 6. The largest upper bound of the 90% CI was 18.2 ms and was observed on Day 8 of the study.

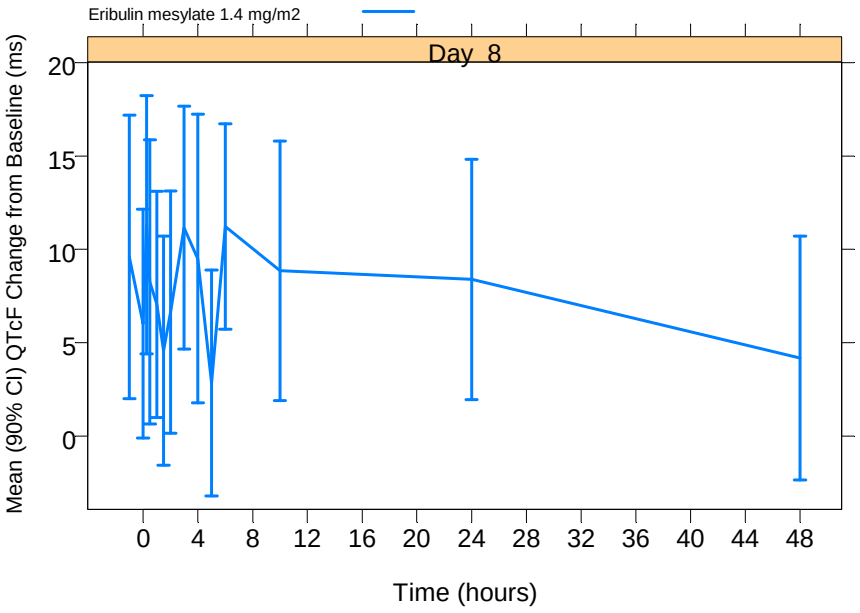
Table 6: Analysis Results of ΔQTcF

	Day1			Day8		
Time	Mean ΔQTcF	Lower 90% CI	Upper 95% CI	Mean ΔQTcF	Lower 90% CI	Upper 90% CI
0	0.1	-3.9	4.1	6.0	-0.1	12.1
0.25	1.7	-2.3	5.7	11.3	4.4	18.2
0.5	0.0	-4.5	4.5	8.3	0.6	15.9
1.0	-0.1	-4.3	4.1	7.0	1.0	13.1
1.5	-0.5	-4.5	3.4	4.6	-1.6	10.7
2.0	0.1	-4.5	4.6	6.6	0.1	13.1
3.0	-0.9	-4.1	2.4	11.2	4.6	17.7
4.0	1.3	-3.0	5.6	9.5	1.8	17.2
5.0	-1.8	-4.8	1.3	2.8	-3.2	8.9
6.0	1.0	-1.9	3.9	11.2	5.7	16.7
10.0	0.0	-6.5	6.4	8.9	1.9	15.8
24.0	-5.6	-12.1	0.9	8.4	2.0	14.8
48.0	-1.8	-8.3	4.6	4.2	-2.4	10.7

The time profile of ΔQTcF on days 1 and 8 is illustrated in **Figure 5**

Figure 5: Mean and 90% CI ΔQTcF Timecourse

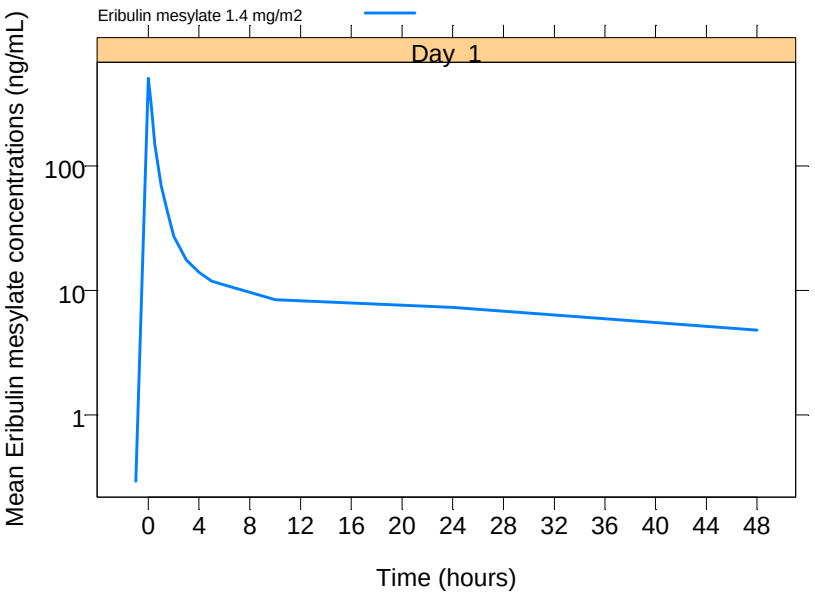


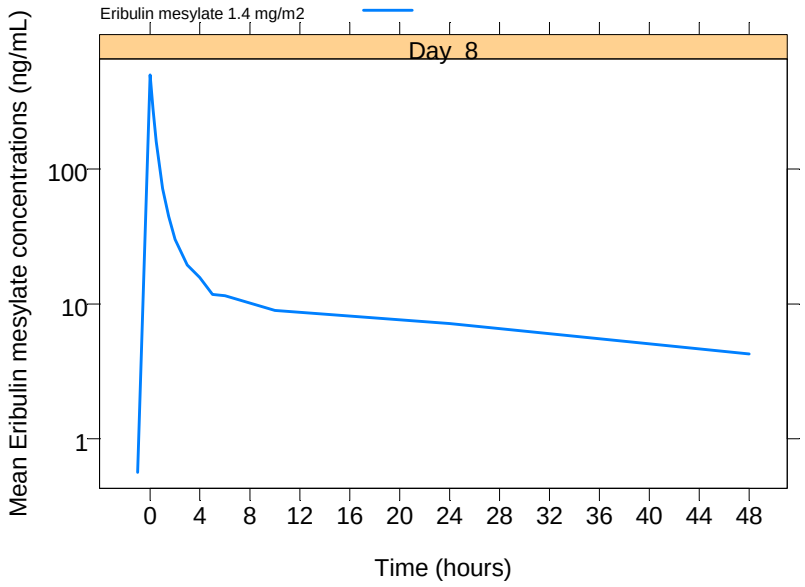


5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile on days 1 and 8 is illustrated in **Figure 6**.

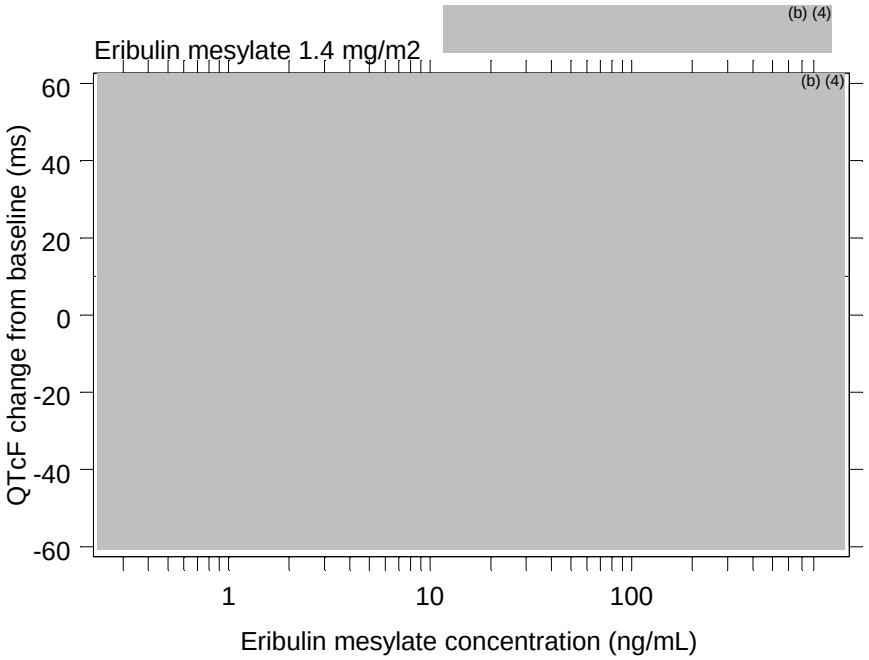
Figure 6: Mean Eribulin Mesylate Concentration-time Profiles for 1.4 mg/m^2 on Day 1 (Top panel) and Day8 (Bottom panel)

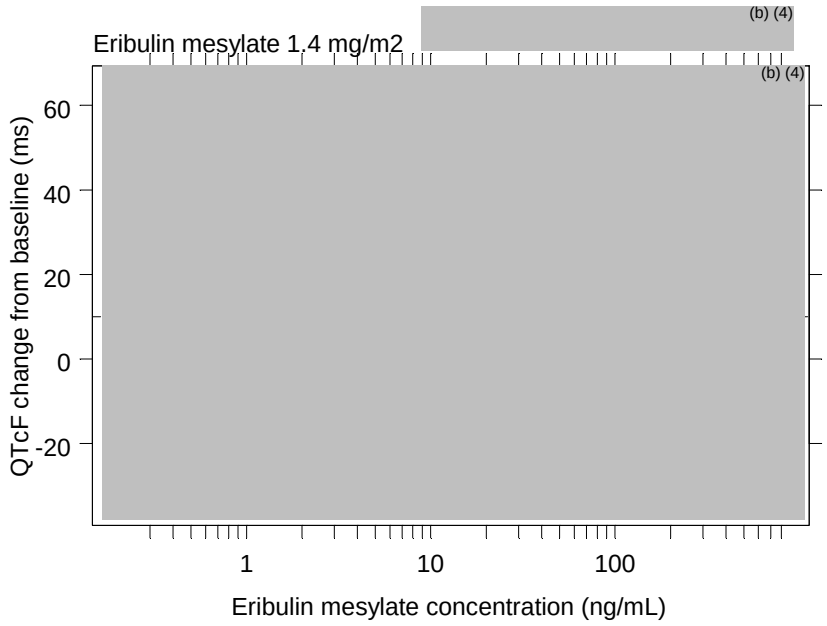




The relationship between ΔQTcF and eribulin mesylate concentrations is visualized in Figure 7. There is no evident exposure-response relationship.

Figure 7: Δ QTcF vs. Eribulin mesylate Concentration on Day 1 (Top panel) and Day 8 (Bottom panel)





5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study during the study phase). The cases of pre-syncope, vertigo and atrial fibrillation have been discussed under section 4.2.8.3.

5.3.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics, around 73% of the ECGs were annotated in the primary lead II with V2 and V5 being alternate leads which is not unexpected in this patient population. Less than 0.6% of ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.3.3 PR and QRS Interval

The sponsor reported no clinically relevant effect on the PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Monotherapy: 1.4 mg/m^2 by IV injection over 2 – 5 minutes on Days 1 and 8 of a 21-day cycle (b) (4)	
Maximum tolerated dose	NCI Study #5730: 1.4 mg/m^2 as an IV bolus injection on Days 1, 8 and 15 of a 28-day cycle Eisai Study E7389-A001-101: 1.0 mg/m^2 as an one hour IV infusion on Days 1, 8 and 15 of a 28-day cycle Eisai Study E7389-A001-102: 2.0 mg/m^2 as an one hour IV infusion on Day 1 of a 21-day cycle Eisai Study E7389-J081-105: 1.4 mg/m^2 as a 5 minute IV infusion on Day 1 and 8 of a 21-day cycle	
Principal adverse events	neutropenia, fatigue, nausea, anemia, alopecia	
Maximum dose tested	NCI Study #5730	2.0 mg/m^2 as an IV bolus injection on Days 1, 8 and 15 of a 28-day cycle
	Eisai Study E7389-A001-101	1.4 mg/m^2 as an one hour IV infusion on Days 1, 8 and 15 of a 28-day cycle
	Eisai Study E7389-A001-102	4.0 mg/m^2 as an one hour IV infusion on Day 1of a 21-day cycle
	Eisai Study E7389-J081-105	2.0 mg/m^2 as a 5 minute IV infusion on Day 1 and 8 of a 21-day cycle
Exposures Achieved at Maximum Tested Dose	*2.0 mg/m^2 as a 5 minute IV infusion*	
	C_{max} (mean)	0.72 µg/ml (E7389-J081-105)
	AUC_{0-inf} (mean)	1.37 µg/ml*hr (E7389-J081-105)
	4.0 mg/m^2 as an one hour IV infusion	
	C_{max} (mean)	0.53 µg/ml (E7389-A001-102)
	AUC_{0-inf} (mean)	2.33 µg/ml*hr (E7389-A001-102)
Range of linear PK	Up to highest doses tested: - 2.0 mg/m^2 given as a IV bolus / 5 min infusion - 4.0 mg/m^2 given as a 1 hour IV infusion	
Accumulation at steady state	No significant accumulation with 1 week separation between dosing intervals.	
Metabolites	Unknown. Metabolites to be identified as part of a planned	

	(b) (4) In preclinical studies in dogs and rats, only a minor contribution of metabolites was found in plasma, urine and feces, with most of the radioactivity accounted for as unchanged drug in feces.	
Absorption	N/A (IV administration)	
Distribution	Mean steady state volumes of distribution for studies NCI5730 and E7389-A001-101 were 47.6 and 55.2 L/m^2, respectively. Human plasma protein binding ranged from 49 to 65% over the 0.1-1 µg/ml range.	
Elimination	Mean clearance values for studies NCI 5730 and E7389-A001-101 were 1.3 L/hr/m^2 and 1.77 L/hr/m^2, respectively. Corresponding mean terminal half-life values were 39 and 38 hrs, respectively.	
Intrinsic Factors	Body size	Dose of eribulin is individualized by body surface area, and exposure is thereby normalized to body size.
	Renal function / impairment	Renal excretion is a minor elimination pathway. Only approximately 5%, 7%, and, 10% of the dose administered was eliminated in the urine as unchanged drug in studies E7389-A001-101, E7389-A001-102, and NCI Study #5730 respectively. Therefore, no significant clinical effect of renal impairment is anticipated.
	Hepatic impairment	This will be determined in a planned clinical study.
	Race	No effects of race on eribulin PK are known. The effect of race will be assessed further in a population PK analysis.
	Age	No effects of age on eribulin PK are known. The effect of age will be assessed further in a population PK analysis.

Extrinsic Factors	Food Effects	N/A (IV administration)
	Drug-drug interactions.	The effects of inhibition and induction of CYP3A4 on E7389 PK will be determined in a planned clinical study. Preclinical metabolic profiling of E7389 indicates a low potential for drug-drug interactions caused by E7389.
Expected High Clinical Exposure Scenario	Patients in study E7389-G001-211 were sampled 5-10 minutes after start of infusion of their first 1.4 mg/m^2 dose of eribulin. Preliminary results of a population PK analysis provide posthoc estimates of the median (range) C_{max} as 0.38 (0.25 – 0.678) µg/ml and AUC as 0.74 (0.24 – 3.53) µg/ml*hr. The dose of eribulin is limited by toxicity, i.e. neutropenia, which is monitored closely. Eribulin treatment is interrupted and/or adjusted downwards in patients experiencing adverse events. In this way, high clinical exposures are expected to be limited by known and manageable toxicity.	

6.2 TABLE OF STUDY ASSESSMENTS

Table 3: Schedule of Assessments for Screening and Study Phase (Cycle 1)

Phase	Screening	Study Phase (Cycle 1)								
Period	Pre-Treatment	Treatment							End of Treatment[g,l]	Follow-up[m]
Assessments	Days -28 to 0	Day 1	Day 2	Day 3	Day 8	Day 9	Day 10	Day 15	Study Termination (Within 30 days of Final Treatment)	(Every 3 months)
Informed Consent	X[a]									
Medical/Surgical history	X									
Tumor Assessments (RECIST)	X[b]								X[l]	X[m]
ECOG performance Status	X	X							X[l]	
Inclusion/Exclusion	X	X								
Demographic Data	X									
Vital signs	X	X[c]			X[c]			X[c]	X[l]	
Physical Exam[d]	X[d]	X[d]			X[d]			X[d]	X[l]	
Triplicate 12-lead ECG[e]	X[e]		X[e]	X[e]		X[e]	X[e]		X[e,l]	
Holter ECG Collections[f]	X	X			X					
PK analysis[g]		X	X	X	X	X	X			
Pregnancy Test (If applicable)[h]	X[h]	X[h]								
Hematology Assessments[i,k]	X	X[i,k]			X[i,k]			X[i,k]	X[l]	
Clinical Chemistry Assessments[j]	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[l]	
Liver Function Tests (LFTs)[j]	X	X[j]			X[j]			X[j]	X[j,l]	
Urinalysis	X	X							X[l]	
Eribulin mesylate (E7389) Administration		X			X					
Prior and concomitant Medications	Recorded Throughout								X[l]	
Prior and concomitant Medical Procedures	Recorded Throughout								X[l]	
Adverse events	Monitored and Recorded Throughout								X[l]	

† These assessments were to be conducted upon early discontinuation from the study (before Cycle 2 Day 1).

a. Informed Consent was to be taken before any study specific procedures. Procedures which were performed as part of routine care and which occurred prior to date of consent were acceptable only if they fell within the allowed screening period.

b. Baseline tumor assessments, consisting of radiologic evaluation of the chest and abdomen including pelvis, were to be performed within 28 days prior to start of treatment. A radio-isotope bone scan was to be performed within 6 weeks prior to start of treatment.

Continued

Phase	Screening	Study Phase (Cycle 1)								
Period	Pre-Treatment	Treatment							End of Treatment[g,l]	Follow-up[m]
Assessments	Days -28 to 0	Day 1	Day 2	Day 3	Day 8	Day 9	Day 10	Day 15	Study Termination (Within 30 days of Final Treatment)	(Every 3 months)

c. Height was to be measured at screening only. Weight to determine BSA for dose calculation was only to be performed on Day 1 pre-dose of Cycle 1. Other vital signs were to be done on Day 1, Day 8 and Day 15 of Cycle 1.

d. A complete physical exam was to be completed at Screening and at Day 1 of Cycle 1. A symptom directed physical exam was to be performed on Days 8 and 15.

e. ECG: Using 12-lead ECG, single ECG during screening was to be at least 96 hours prior to Day 1, for eligibility. Triplicate ECG recordings for Cycle 1 Days 2, 3, 9, and 10 and End of Treatment visit (if applicable) were to be taken. ECGs (Triplicate) on Days 1 and 8 were to be extracted from continuous Holter readings just prior to blood sample collection. Patients wee to be recumbent for a period of approximately 10 minutes before each reading was taken.

f. Continuous time-matched Holter-ECG's were to be collected on the day prior to first administration of eribulin mesylate (Day 0) and at Days 1 and 8. Individual ECGs (triplicate) were to be extracted from the recordings at predose, end of eribulin mesylate infusion, 15mins, 30mins, 1, 1.5, 2, 3, 4, 5, 6, 10 and 24 hours after start of eribulin mesylate administration. Patients were to be recumbent for a period of approximately 10 minutes before each timepoint. If possible, patients were to be encouraged to eat the same or similar food at the same time on all days that the Holter ECGs were conducted.

g. Blood for PK analysis was to be collected on Cycle 1, Days 1 and 8 predose, end of eribulin mesylate infusion, 15 min, 30min, 1, 1.5, 2, 3, 4, 5, 6 hours and 10 hours after start of eribulin mesylate administration. Blood for PK analysis was also to be obtained on Cycle 1, Day 2 and Day 9 (24 hours) and Day 3 and Day 10 (48 hours) after start of eribulin mesylate administration. A 20% time window (±20% from each timepoint) for each timepoint up to 1 hour and a 10% time window (±10% from each timepoint) for all timepoints thereafter were allowed for these assessments.

h. Urine or serum pregnancy tests were to be performed at screening and pre-dose Day 1 Cycle 1 for all female patients. If screening pregnancy test was within 72 hours prior to drug administration, pregnancy test did not need to be repeated at Day 1 Cycle 1. An unscheduled pregnancy test was to be performed at any point during the study if a female patient thought she may be pregnant.

i. Hematology laboratory assessments were to be reviewed prior to drug administration. Assessments scheduled on Day 1 of Cycle 1 could be performed within 72 hours prior to the Day 1 of Cycle 1 visit. Assessments scheduled on Day 8 and Day 15 could be performed within 24 hours prior to scheduled visit.

j. Clinical Chemistry and Liver Function laboratory assessments were to be reviewed prior to drug administration. Screening assessments could be performed within 72 hours prior to Day 1 Cycle 1, and Day 15 could be performed within 24 hours prior to scheduled visit. Clinical Chemistry assessments scheduled on Days 1, 2, 3, 8, 9 and 10 had to be performed on the same day as ECG assessments.

k. If neutropenia or thrombocytopenia ≥ Grade 3 occurred, complete blood count with differential and AE assessment was to be repeated at least every 3 days (until improvement to < Grade 3).

l. End of treatment visits were to be performed for patients that discontinued from the study within or after the Study phase (Cycle 1) and never entered the Extension phase. All patients that continued in the trial were to proceed with visits in the Extension phase as detailed in the Schedule of Assessments for the

Phase	Screening	Study Phase (Cycle 1)								
Period	Pre-Treatment	Treatment							End of Treatment[b]	Follow-up[a]
Assessments	Days -28 to 0	Day 1	Day 2	Day 3	Day 8	Day 9	Day 10	Day 15	Study Termination (Within 30 days of Final Treatment)	(Every 3 months)

Extension phase Period.

Continued

[a] Follow-up was to be performed for patients who came off study without progressive disease during or after the Study phase (Cycle 1) and never entered the Extension phase of the study. Disease evaluation was to be performed every 3 months. The radiologic scans during follow-up only reflected the burden of disease defined at baseline, unless suspicion of disease at other sites.

Abbreviations are explained in the abbreviations table in Section 4.

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/

HAO ZHU
06/22/2010

Anshu Marathe
06/22/2010

DEVI KOZELI on behalf of SUCHITRA M BALAKRISHNAN
06/22/2010

NORMAN L STOCKBRIDGE
06/22/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 201532/0 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE- N/A
Proprietary Name: Halaven Established/Proper Name: Eribulin mesylate injection Dosage Form: Single Use Vial Strengths: 1.0 mg eribulin mesylate per vial in 2 mL of solution. Concentration- 0.5mg/ml		
Applicant: Eisai, incorporated Agent for Applicant (if applicable): N/A		
Date of Application: March 30, 2010 Date of Receipt: March 30, 2010 Date clock started after UN:		
PDUFA Goal Date: September 30, 2010	Action Goal Date (if different):	
Filing Date: May 28, 2010	Date of Filing Meeting: May 3, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]	

☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 67193	

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			Proprietary name has not been approved yet
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☐ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*			**X**	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			Form is signed by Director of Finance and Accounting from Eisai, Inc
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X			

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***			X	

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?				NOT YET
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***				

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? EOP2 and EOP2 follow-up meeting **Date(s):** April 14, 2006, March 27, 2008 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 23, 2007 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 3, 2010

BLA/NDA/Supp #: 201532/0

PROPRIETARY NAME: Halaven

ESTABLISHED/PROPER NAME: Eribulin Mesylate Injection

DOSAGE FORM/STRENGTH: Dosage Form: Single Use Vial
Strengths: 1.0 mg eribulin mesylate per vial in 2 mL of solution. Concentration- 0.5mg/ml

APPLICANT: Eisai, Incorporated

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane

BACKGROUND: Eisai Inc. has submitted a New Drug Application (NDA) for eribulin mesylate, new molecule entity on March 30, 2010, received by FDA on March 30, 2010. Eribulin mesylate Injection is indicated 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. Since January 2003, the clinical development of eribulin mesylate has been conducted under IND 67,193.
Eisai Inc. is requesting a **Priority Review** based on the achievement of statistical significance of the endpoint of Overall Survival and their request has been granted. The PDUFA date is September 30, 2010

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Vaishali Jarral	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Steven Lemery		Y
Clinical	Reviewer:	Martha Donoghue	Y

	TL:	Steven Lemery	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Stacy Shord	Y
	TL:	Hong Zhao	N
Biostatistics	Reviewer:	Weishi Yuan	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Lori Kotch	Y
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Ying Wang	Y
	TL:	Liang Zhou	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Bob Mello	Y
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Shawn Gould	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Loretta Holmes	Y
	TL:	Kristina Toliver	N
OSE/DRISK (REMS)	Reviewer:	John Hubbard	Y
	TL:	Mary Dempsey	N
Bioresearch Monitoring (DSI)	Reviewer:	Lauren Iacono-Connors	Y
	TL:		

Other reviewers		
Other attendees	Patricia Keegan, Division Director, Division of Biologic Oncology Products Scott Goldie, RPM from ONDQA	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☒ YES Date if known: September 1-2, 2010 ☐ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Comments:	

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	N/A ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Richard Pazdur, Director, Office of Oncology Drug Products **21st Century Review Milestones (see attached)** (optional): **Comments**: Also see filing Meeting Minutes of May 3, 2010. Milestones are included in the meeting minutes	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

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

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

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

DSI CONSULT: Request for Clinical Inspections

Date: April 12, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Lauren Iacono-Connor, M.D., Regulatory Director
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Martha Donoghue, Medical Officer, OODP/DBOP
Steven Lemery, Team Leader, OODP/DBOP
Patricia Keegan, M.D. Director, DBOP

From: Vaishali Jarral, Regulatory Project Manager, OODP/DBOP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 201532/0
Applicant/ Applicant contact information (to include phone/email):
Eisai, Inc.
Contact: 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

Drug Proprietary Name: Halaven [eribulin mesylate injection (generic)]
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Priority
Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of patients with locally advanced or metastatic breast cancer who have received two or more chemotherapeutic regimens, including an anthracycline and a taxane.

PDUFA:
Action Goal Date: September 30, 2010
Inspection Summary Goal Date: August 30, 2010

II. Protocol/Site Identification

The pivotal study [Study E7389-G000-305 (The 'EMBRACE' Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. 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) was conducted in North America Europe (West and East), and Latin America. The study was an industry sponsored study.

We request site inspections at the following sites (in descending order of priority). Note that protocol deviations below refer to major inclusion criteria protocol deviations:

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
2815 – Dr. Joanne L. Blum US Oncology ** 3535 Worth Street Sammons Cancer Center Collins Building Dallas, TX 75246 PI phone: 214-370-1000	E7389-G000-305	21	5 protocol deviations; median overall survival (OS) for eribulin arm 35 days greater than the physicians' choice (TPC) arm.
2008 – Dr. Javier Cortes Hospital Vall d'Hebron Unitat de cancer de mama, planta 1, Edifici Materno-Infantil Paseo Vall d'Hebron, 119-120 08035 Barcelona Spain PI phone: +34 93 489 43 50 PI email: jacortes@vhebron.net	E7389-G000-305	34	Highest enrolling site; 4 protocol deviations. Median OS for eribulin arm 93 days greater than TPC arm.
2812 - Dr. Han A. Koh Bellflower Satellite 9400 East Rosecrans Avenue, Module 3200 Kaiser Permanente –Bellflower Bellflower 90706 US PI Phone – (562) 461-6941	E7389-G000-305	18	1 protocol deviation; median OS for eribulin arm 182 days greater than TPC arm.
1401 – Dr. Philippe Bougnoux Hopital Bretonneau Service CORAD 2 Boulevard Tonnelle 37044 Tours Cedex France PI Phone: +33(0)2 47 47 80 75 PI email:bougnoux@med.univ-tours.fr	E7389-G000-305	17	5 protocol deviations; median OS for eribulin arm 185 days greater than TPC arm.
1402 – Dr. Thierry Delozier Centre Francois Baclesse Caen Avenue Du General Harris BP 5026 14076 Caen Cedex 05 France PI phone: 02.31.45.50.15 PI fax: 02.31.45.50.57	E7389-G000-305	19	1 protocol deviation; median OS for eribulin arm 245 days greater than TPC arm

The following sites are also US Oncology sites in or near Dallas, TX with protocol deviations that are of interest (but of lower priority than those listed above):

2829 – US Oncology 7777 Forest Lane Bldg. D400 Dallas, TX 75230-2510	E7389-G000-305	8	3 protocol deviations
2828– US Oncology 910 E. Houston Street Suite 100 Tyler, TX 75702	E7389-G000-305	10	1 protocol deviation

Additional Note: Applicant also mention (b) (4) associated with Study 305. Here is the additional information from the applicant regarding this CRO:

"The Toro (TRANSFER OF OBLIGATION) in the NDA refers to the (b) (4), office which holds our CRO contract with (b) (4) The clinical documentation is held in the (b) (4) by the study manager and project team. .It is quite common that the clinical documentation is held by the study team rather than by headquarters."

III. Site Selection/Rationale

This DSI consult request is to assist in the evaluation of data integrity for a new drug application for a new molecular entity. The sites were chosen based upon an analysis of site-specific efficacy data, number and types of protocol deviations, and patient number enrolled at each site.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- X Enrollment of large numbers of study subjects
- X High treatment responders (specify):
- X Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- X Other (specify): substantial protocol violations that may be pertinent to efficacy analysis

International Inspections:

Reasons for inspections (please check all that apply):

- X There are insufficient domestic data
- ____ Only foreign data are submitted to support an application
- ____ Domestic and foreign data show conflicting results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- X Enrollment of large numbers of study subjects, site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study.

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: Although of lesser priority, we included two additional domestic sites because they are branches of the same organization (U.S. Oncology) as site 2815 and are also located in or near Dallas.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable): Not applicable.

Should you require any additional information, please contact Vaishali Jarral at 301-796-4248 or Martha Donoghue *at* 301-796-5284.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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
04/19/2010

PATRICIA KEEGAN
04/20/2010

PATRICIA KEEGAN on behalf of STEVEN J LEMERY
04/20/2010

MARTHA B DONOGHUE
04/20/2010

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

Memorandum

DATE: April 5, 2010

FROM: Patricia Keegan, M.D.
Director
Division of Biological Oncology Products
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Designation of NDA application review status
Sponsor: Eisai, Incorporated
Product: Eribulin mesylate (Injection)
Indication: Treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and taxane.

TO: NDA 201532

The review status of this file submitted as a NDA application is designated to be:

☐ Standard (10 Months) ☒ Priority (6 Months)

Patricia Keegan, M.D.:_____

{See appended electronic signature page}

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
04/05/2010

PATRICIA KEEGAN
04/27/2010