

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201532

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	11/09/2010
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA # 201532
Applicant	Eisai, Inc.
Date of Submission	March 30, 2010
PDUFA Goal Date	September 30, 2010; December 30, 2010 following major amendment
Proprietary Name / Established Name	Halaven Injection (eribulin mesylate)
Dosage forms / Strength	Halaven Injection 1 mg/2 mL (0.5 mg/mL)
Proposed Indication(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.
Recommended:	<i>Approval</i>

Table of Contents

1. Introduction.....	3
2. Background.....	3
3. CMC.....	6
3.1 General product quality considerations	6
3.1.1 Drug substance.....	6
3.1.2 Drug product	8
3.2 Facilities review/inspection	9
3.3 Microbiology.....	9
4. Nonclinical Pharmacology/Toxicology	10
4.1 General nonclinical pharmacology/toxicology considerations.....	10
4.2 Carcinogenicity	11
4.3 Reproductive toxicology.....	11
4.4 Other notable issues	11
5. Clinical Pharmacology/Biopharmaceutics.....	11
5.1 General clinical pharmacology/biopharmaceutics considerations.....	12
5.2 Drug-drug interactions.....	12
5.3 Pathway of elimination	12
5.4 Evaluation of intrinsic factors potentially affecting elimination	12
5.5 Demographic interactions/special populations	13
5.6 Thorough QT study or other QT assessment	13
6. Clinical Microbiology.....	13
7. Clinical/Statistical- Efficacy	13
7.1 Background of clinical program	14
7.2 Design of efficacy studies.....	14
7.3 Study results.....	16

8. Safety	20
8.1 Adequacy of database, major safety findings	20
8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests	20
8.3 Immunogenicity	22
8.4 Special safety concerns	22
8.5 Discussion of primary reviewer’s comments and conclusions	23
8.6 Highlight differences between CDTL and review team with explanation for CDTL’s conclusion and ways that the disagreements were addressed	23
8.7 Discussion of notable safety issues (resolved or outstanding).....	23
9. Advisory Committee Meeting.....	23
10. Pediatrics.....	23
11. Other Relevant Regulatory Issues.....	24
11.1 Application Integrity Policy (AIP).....	24
11.2 Financial disclosures.....	24
11.3 GCP issues	24
11.4 DSI audits.....	24
11.5 Other discipline consults.....	25
11.6 Other outstanding regulatory issues.....	25
12. Labeling	25
12.1 Proprietary name.....	25
12.2 Labeling issues raised by DDMAC	25
12.3 Physician labeling.....	26
12.4 Major issues not resolved.....	27
12.5 Carton and immediate container labels.....	28
12.6 Patient labeling/Medication guide	28
13. Recommendations/Risk Benefit Assessment.....	28
13.1 Recommended regulatory action	28
13.2 Risk-benefit assessment	28
13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies..	29
13.4 Recommendation for other postmarketing requirements and commitments	29

Table of Figures

Figure 1: Chemical Structure of Eribulin Mesylate.....	7
Figure 2: K-M Curve for OS in Study 305	18
Figure 3: K-M Curve for Updated OS Results in Study 305.....	19

Table of Tables

Table 1: Pre-Submission Regulatory History of Eribulin.....	4
Table 2: DS and DP Manufacturing Sites.....	9
Table 3: Therapies Assigned and Administered to Patients in the Control (TPC) Arm.....	17
Table 4: OS Analysis (ITT population)	17
Table 5: Updated OS Results (ITT) Population.....	18

1. Introduction

Eisai submitted New Drug Application (NDA) 201532 on March 30, 2010 for eribulin mesylate (proposed trade name, Halaven Injection) for the treatment of patients with locally advanced or metastatic breast cancer who have received at least two chemotherapy regimens, including an anthracycline and a taxane. Eribulin is a cytotoxic microtubule inhibitor derived from and is a synthetic analogue of halichondrin B.

To support this NDA, the Applicant primarily relied on the results of a single randomized (2:1) trial, Study E7389-G000-305 (or Study 305) that evaluated the treatment effects of eribulin mesylate versus active control treatment chosen at the discretion (pre-randomization) of the investigator. Study 305 demonstrated a statistically significant improvement in overall survival among women with metastatic breast cancer treated with eribulin.

The following important issues were considered during the review of this application:

Clinical/Statistical: The primary issue considered during the review of this application was whether the results of a single adequate and well-controlled trial (with supportive evidence from single-arm studies) were sufficient to support approval. Ultimately, the primary clinical and statistical reviewers recommended approval based on the results of Study 305 (see Section 7 below). An additional issue considered during the clinical part of the review was the choice of the Study 305 control arm (single agent therapy chosen by the investigator).

Clinical Safety/Safe Use: Study 305 demonstrated a statistically significant improvement in overall survival, an endpoint encompassing both safety and effectiveness. Adverse events observed following eribulin treatment were similar to adverse events that are commonly associated with other microtubule inhibitors (i.e., neutropenia and neurotoxicity).

Additional considerations regarding safe use in special populations (i.e., patients with renal insufficiency and impaired hepatic function) were identified by clinical pharmacology review staff and are described in Section 6 of this review.

Product: Eribulin mesylate is a complex chemical entity and has a chiral structure with (b) (4). The primary drug substance is (b) (4). The synthesis of eribulin requires (b) (4). The major issue regarding the CMC review of eribulin involved the selection of the appropriate starting materials.

2. Background

Eribulin mesylate (eribulin) is a microtubule inhibitor originally derived from and is a synthetic analogue of halichondrin B, a product isolated from *Halichondria okadai* (a sea sponge). Eribulin represents a new class of microtubule inhibitors with a different tubulin binding site compared to taxanes or vinca alkaloids. According to the Applicant, eribulin “inhibits the growth phase of microtubule dynamics without affecting the shortening phase and sequesters tubulin into non-productive aggregates.” Differences in effects between microtubule-binding drugs may be related to differences in binding sites of the different drug

classes: eribulin binds to plus (+) ends of microtubules; vinca alkaloids bind to plus (+) ends and along the sides of microtubules; and taxanes and epothilones bind to the beta subunits at the inside surface of microtubules. Despite differences in tubulin binding sites, some of the adverse reactions common to vinca alkaloids and taxanes (i.e., myelotoxicity and peripheral neuropathy) also frequently occur following eribulin treatment.

The Applicant proposed the following indication for eribulin: treatment of patients with locally advanced or metastatic breast cancer who have received at least two chemotherapy regimens, including an anthracycline and a taxane. Eisai based the request for approval on a treatment effect on overall survival. Up to this date, no initial approvals in the anthracycline and taxane-refractory population of women with metastatic breast cancer have been based on an improvement in overall survival; although capecitabine subsequently demonstrated an effect on OS in women with breast cancer following anthracycline-containing therapy in combination with docetaxel. Docetaxel received regular approval based on an improvement in OS in women with breast cancer who received prior anthracycline therapy.

The ultimate goal of chemotherapy treatment is to prolong and improve quality of life. With this goal in mind, in the absence of strong evidence that combination therapy is superior to single agent therapy, the majority of clinicians treat patients with refractory metastatic breast cancer with single agent chemotherapy (an exception may be anti-HER2 combination therapy in women with HER2-positive disease). Single drug therapy regimens commonly administered to women with metastatic breast cancer who previously received an anthracycline and a taxane include capecitabine, gemcitabine, and vinorelbine. These three drugs were the most commonly administered drugs to patients in the control arm of Study 305. A more detailed discussion of the control arm of Study 305 is described in Section 7 below.

The following table describes the regulatory history of eribulin prior to this NDA submission.

Table 1: Pre-Submission Regulatory History of Eribulin

Date	Nature of Regulatory Activity	Issues Described in Meeting, Submission, or Letter
3/31/2003	IND submitted	<ul style="list-style-type: none"> • IND 67,193 submitted to DDOP for review
9/2/2005	EOP2 meeting	<ul style="list-style-type: none"> • The population of patients who received at least 2 therapies but no more than four (Her2+ patients must have received trastuzumab) represents an unmet medical need (<i>however, FDA warned Eisai that available therapy could change</i>). • Regarding Study 301 (a different randomized controlled trial), acceptability of PFS as an endpoint would depend upon the magnitude of the difference and tolerability profile of eribulin. • FDA would require an independent review of radiographs in order to consider PFS as the primary endpoint. • Study 301 should be powered to demonstrate an effect on OS.
2/28/2006	IND letter regarding SPA	<ul style="list-style-type: none"> • SPA agreement reached regarding Study 301.

Date	Nature of Regulatory Activity	Issues Described in Meeting, Submission, or Letter
3/7/2006	Faxed communication to Eisai	<ul style="list-style-type: none"> • Non-clinical data package appeared adequate to support an NDA. • Embryo-fetal development studies in rabbits not necessary if rat studies demonstrate an effect on fetal development. • Organ dysfunction and drug-drug interactions studies should be conducted during drug development.
4/14/2006	Type B CMC meeting	<ul style="list-style-type: none"> • Discussion held with Eisai regarding starting materials used in the manufacturing process. • FDA stated that the starting materials currently used in the manufacturing process were not acceptable.
1/22/2007	Faxed communications of FDA answers to Eisai submission regarding Study 305	<ul style="list-style-type: none"> • FDA stated that patients who were HER-2 positive should receive prior treatment with trastuzumab. • FDA expressed concern regarding whether Study 305 could support full approval because of the use of different therapies in the control arm. • FDA recommended the selection of a limited number of regimens for the control arm, and that FDA may require review of the results of Study 301.
8/21/2007	Fast track designation	<ul style="list-style-type: none"> • Fast track designation granted for the following reasons: (1) Locally advanced or metastatic breast cancer refractory to or relapsed after treatment with standard therapy, and (2) Eribulin demonstrates antitumor activity in patients with locally advanced or metastatic breast cancer refractory to or relapsed after treatment with standard therapy.
8/23/2007	pre-NDA meeting	<ul style="list-style-type: none"> • FDA and Eisai agreed upon the content of an NDA package. • FDA cautioned that an ORR of (b) (4) % appeared low and whether this effect size would support approval in a single-arm study would be a review issue.
12/14/2007	Telephone conference	<ul style="list-style-type: none"> • An NDA for AA based on response rate in single-arm trials would not be acceptable because eribulin was not better than available therapy at the time of the proposed NDA submission.
12/20/2007	Telephone conference to discuss Study 301	<ul style="list-style-type: none"> • FDA stated that proposed changes to the statistical analysis plan (SAP) of Study 301 were not acceptable and would render the SPA agreement invalid (including the interim analysis of PFS and plan for a non-inferiority analysis of OS). • Based on FDA advice, Eisai revised the SAP based on FDA recommendations and FDA sent a communication on 5/13/2008 that the changes would adequately support a regulatory submission.

Date	Nature of Regulatory Activity	Issues Described in Meeting, Submission, or Letter
3/21/2008	EOP2 meeting comments from FDA to Eisai	<ul style="list-style-type: none"> FDA expressed concern that Study 305 may not be sufficiently robust to support NDA approval. The following would be review issues if the results from Study 305 were submitted in support of an NDA: whether TPC has an adverse impact on survival; and whether the results of Study 305 alone would support approval. FDA requested clarification regarding whether appropriate patients received trastuzumab.
7/3/2008	Amendment to the IND regarding Study 305	<ul style="list-style-type: none"> Proposal to increase sample size based on a pre-planned sample size reassessment. Event number smaller than expected and sample size increased from 630 to 1,000 (acceptable per FDA statistical review of the amendment). Target number of events unchanged (i.e., 411 deaths).
12/10/2008	Email to Eisai reg. Nov 21, 2008 submission to IND	<ul style="list-style-type: none"> FDA recommended against an early interim administrative look at the data from Study 305 to ensure the integrity of the study was not compromised.
11/23/2009	Type B pre-NDA meeting	<ul style="list-style-type: none"> Agreements reached on the content of an NDA application.

3. CMC

ONDQA recommended approval of eribulin from the chemistry, manufacturing, and control perspective. The overall review of eribulin mesylate was challenging from a CMC perspective because of the complexity of the molecule (b) (4) and the complexity of the manufacturing process (b) (4). In order to ensure that eribulin mesylate could be adequately characterized (numerous (b) (4) impurities are possible during DS manufacturing), the CMC review emphasized the synthesis process and process controls, especially regarding starting materials and intermediates.

Ultimately the ONDQA review found the following to be acceptable: DS and DP information; revised DS and DP specifications; analytical method validation; revised starting materials; inclusion of additional in-process controls; and addition of chiral assay testing for starting materials.

3.1 General product quality considerations

3.1.1 Drug substance

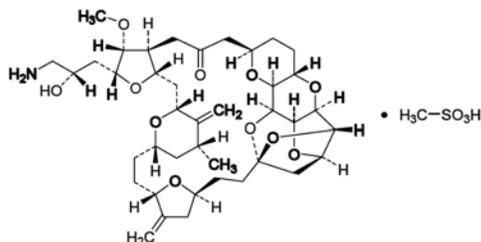
The eribulin drug substance is a single enantiomer with (b) (4) and is a synthetic analogue of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*.

The chemical name for eribulin mesylate is 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one,

2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-, (2*R*,3*R*,3*aS*,7*R*,8*aS*,9*S*,10*aR*,11*S*,12*R*,13*aR*,13*bS*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29*aS*)-, methanesulfonate (salt).

Eribulin mesylate has the empirical formula of $C_{40}H_{59}NO_{11} \cdot CH_4O_3S$, and a molecular weight of 826.0 (729.9 for free base). The following figure, copied from the ONDQA review, shows the chemical structure of eribulin mesylate.

Figure 1: Chemical Structure of Eribulin Mesylate



As described above, the major issue of concern during the CMC review of the eribulin mesylate DS involved the selection of the appropriate starting materials. The starting materials proposed at the time of the original NDA submission, were (b) (4)

(b) (4) in the DS of eribulin mesylate. ONDQA originally recommended the designation of (b) (4) as starting materials during an April 14, 2006 end-of-phase 2 meeting in order to maintain control over (b) (4) and the identity of the final drug substance.

During the review cycle, ONDQA notified Eisai by letter on May 13, 2010 that the appropriate starting materials should be those identified by FDA during the April 14, 2006 meeting with the Agency. Based on the May 13, 2010 letter, Eisai requested to meet with FDA and submitted questions to FDA by email on May 26, 2010 regarding the selection of the proposed starting materials. FDA reiterated in a June 9, 2010 letter that the proposed starting materials were not acceptable and that further discussion regarding starting materials would be considered only if “substantial additional information pertaining to the proposed starting materials” were submitted. FDA also reiterated in the June 9, 2010 letter that the appropriate starting materials were (b) (4) and that the key intermediates need to have good manufacturing quality control.

FDA and Eisai held a meeting to discuss the starting materials on July 2, 2010. FDA stated that without re-designating the starting materials,

- there would not be adequate control of impurities during the manufacturing process;
- manufacturing process steps (b) (4) the designation of starting materials would not be regulated and could be changed without notification of regulatory authorities; and
- analytic methods for impurities did not include chiral methodologies and that the NDA did not include detailed data regarding impurity purging strategies.

During the meeting, Eisai agreed to revise the starting materials as recommended by the Agency. FDA required that Eisai submit information regarding the new starting materials necessary to support approvability of the application. Because Study 305 (see Section 7 below) demonstrated an improvement in overall survival, FDA agreed that some of the steps necessary to revise the starting materials could be completed as a post-marketing commitment (i.e., providing results of in-process testing from the manufacturing of each of the isolated intermediates) rather than delaying patients access to eribulin mesylate.

Eisai submitted a quality information amendment on July 28, 2010 in order to provide information requested by FDA regarding the manufacture of the drug substance. Eisai submitted an additional amendment to the NDA on August 9, 2010 containing information pertaining to the newly designated starting materials. Due to the extent of information contained within these submissions, FDA designated that these submissions would constitute a major amendment on August 25, 2010.

Subsequently, ONDQA determined that the July 28, 2010 and August 9, 2010 submissions constituted a partial response to CMC information previously requested by FDA. Rather than issuing a CR letter based on the partial response submitted towards the end of the review cycle, the review team acknowledged the survival benefit conferred by eribulin and made additional efforts to obtain the necessary information (if available) regarding the starting materials for eribulin mesylate. Subsequently, FDA sent an information request letter to Eisai on August 30, 2010 to request the necessary data pertaining to the manufacture of the drug substance of eribulin including data regarding DS impurities and acceptance criteria. Eisai submitted additional quality information amendments on September 16, 2010 and September 24, 2010. Based on the review of these amendments, ONDQA review staff found the data acceptable and recommended approval of eribulin mesylate from a CMC perspective.

3.1.2 Drug product

Eribulin mesylate DP is formulated as a sterile, clear, colorless aqueous solution intended for addition to 100 mL of 0.9% sodium chloride injection, USP for intravenous infusion. The DP is not recommended to be diluted in solutions containing dextrose; product labeling contains this information. The proposed drug product contains 1 mg of eribulin mesylate in 2 mL of ethanol-water (5:95 v/v) and is presented in a (b) (4) vial with a (b) (4) stopper and (b) (4) seal. Excipients are pharmaceutical grade and meet NF/EP/JP compendial requirements. The NDA contained data to address the effects of pH and temperature on eribulin (solubility and stability). Refer to the CMC review for specific information pertaining to impurities, acceptance levels, and qualification based on non-clinical studies.

3.2 Facilities review/inspection

The Office of Compliance issued an overall acceptable recommendation on September 29, 2010 for all manufacturing and testing facilities that were inspected during the review cycle.

ONDQA review staff identified the following manufacturing sites:

Table 2: DS and DP Manufacturing Sites

Manufacturer	DS or DP	Responsibilities
Kashima Plant, Eisai Co., Ltd. Kamisu-shi, Japan	Eribulin mesylate DS	Manufacturing, packaging, release testing, stability testing
(b) (4)		
(b) (4)		
Nerviano Medical Sciences Nerviano, Italy	DP	Manufacturer, release testing
Eisai Inc. Research Triangle Park, NC	DP	Stability and release testing
(b) (4)		
Eisai Inc. Research Triangle Park, NC	DP	Secondary packaging and labeling

3.3 Microbiology

The microbiology review team recommended approval of eribulin. ONDQA requested an assessment by quality microbiology staff as part of the ONDQA initial quality assessment on April 30, 2010. ONDQA requested the reviewing microbiologist to confirm the proposed maximum level of endotoxins for drug product specification. The quality microbiology review team confirmed the following processes relating to product quality microbiology.

- Bioburden samples obtained (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

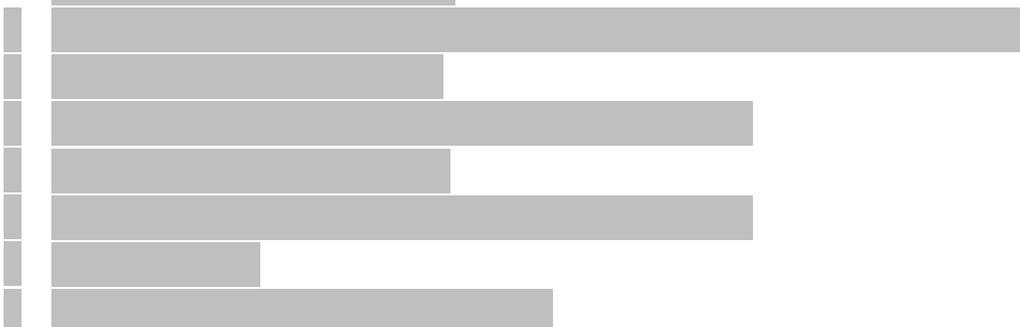
(b) (4)

Liquid immersion microbial challenge was used to test containers (container-closure system). Over 300 vials were tested after filling with tryptic soy broth medium to cover the closure and then challenged with *E. coli*. No bacterial growth occurred in the immersed seals (growth occurred in positive control vials). No sterility failures occurred to date.

An assessment of the manufacturing process including the following were conducted and found to be acceptable in regards to effects on sterility:

- Building and facilities
- Overall manufacturing operation including (b) (4) periods
- (b) (4) of containers, closures, equipment and components
- Environmental monitoring including water systems

An assessment of the process validation including the following were conducted and found to be acceptable in regards to effects on sterility:

- (b) (4)
- 

An assessment of the control of drug product including the following were conducted and found to be acceptable in regards to effects on sterility:

- Specifications including sterility and bacterial endotoxins
- Analytical procedures for endotoxin, sterility, and microbial limits

Finally, the Applicant committed to acceptable post approval stability protocols and stability commitments regarding container closure integrity at release and expiry, endotoxin at lot release, and microbial limits.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer stated in her review that there were no pharmacology/toxicology issues that precluded the approval of eribulin mesylate for the requested indication.

4.1 General nonclinical pharmacology/toxicology considerations

Safety Pharmacology Assessments

The pharmacology/toxicology review contained the following conclusions based on safety pharmacology studies:

- Eribulin produced no inhibition of HERG tail current in HEK293 cells.
- Eribulin (up to 30µM) did not produce an effect on cardiac action potentials in isolated dog Purkinje fibers.
- Eribulin transiently decreased diastolic blood pressure and heart rate in male and female dogs.
- Axonopathy occurred in mice following IV eribulin dosing three times weekly at doses ≥ 1.31 mg/kg.

Repeat-dose Toxicology Studies

Repeat-dose toxicology studies were conducted in both rats and dogs. The Applicant reported toxicity primarily in hematopoietic organs, testes, liver, and nerves (in rats). Non-reversible testicular effects occurred in both rats and dogs at doses lower than the proposed human dose. Doses $\geq 1.2 \text{ mg/m}^2$ were lethal in the 29 day rat study and all doses tested in the rat chronic toxicology study. The end-of-treatment effects were not observed in the 29 day dog study or chronic dog and rat studies since all animals were terminated at the end of the recovery period.

Genetic-toxicology studies

A 5178Y/TK Mouse Lymphoma Mutagenesis assay indicating gene mutation/chromosomal damage and function loss was positive. Additionally, the *in vivo* rat micronucleus assay was strongly positive indicating the potential for induction of chromosomal damage.

4.2 Carcinogenicity

The Applicant did not conduct specific carcinogenicity studies because eribulin is intended to be administered to patients with metastatic breast cancer (life-threatening malignancy). See *genetic-toxicology studies* above for *in-vitro* assays regarding genetic-toxicology (implying the potential for carcinogenicity).

4.3 Reproductive toxicology

The Applicant submitted the results of embryonic fetal development study LFA00033 that confirmed the teratogenic potential of eribulin in rats at doses lower (0.42X) than the proposed dose in humans (1.4 mg/m^2). The findings of external and soft tissue malformations were expected based on the mechanism of action of eribulin (inhibition of microtubule formation). Rat fetal malformations included agnathia, small oral opening, absent tongue, absent stomach, and absent spleen. Additional malformations at different doses included non-ossified sternal centrum, cervical ribs, dilatation of renal pelvis, and bifid centrum of a thoracic vertebrae. The proposed label contains information that eribulin is expected to cause fetal harm when administered to pregnant women.

4.4 Other notable issues

Pharmacology/toxicology reviewers recommended that Eisai adjust the acceptance criteria for impurities for the drug substance and drug product as follows:

- Drug Substance – The acceptance criteria for (b) (4) should be adjusted to (b) (4) and (b) (4) should be adjusted to (b) (4).
- Drug Product – The acceptance criteria for (b) (4) and (b) (4) should be adjusted to NMT (b) (4).

5. Clinical Pharmacology/Biopharmaceutics

Overall, the review staff from the Office of Clinical Pharmacology found that the clinical pharmacology data in NDA 201532 were acceptable for approval.

5.1 General clinical pharmacology/biopharmaceutics considerations

As described in the clinical pharmacology review, rich pharmacokinetic (PK) samples were available from 125 patients enrolled into eight studies and sparse PK sampling was available from 211 patients enrolled into one phase 2 study. Because eribulin is administered intravenously, food is not expected to alter the PK profile of eribulin. The Applicant stated that the PKs of eribulin follow a three compartment model with linear elimination. The C_{max} of a single 1.4 mg/m² dose of eribulin varied from 186 to 207 ng/ml in two separate studies. The t^{1/2} of a single dose of 1.4 mg/m² was 36.1 and 45.6 hours in two separate studies. AUC (0-∞) varied from 600 ng*h/mL to 971 ng*h/mL in the two studies after a single dose of 1.4 mg/m². The pharmacokinetic profile observed following multiple doses of eribulin (on days 1 or 15) was similar to the PK profile following a single dose (refer to Table 6 of the clinical pharmacology review) and no accumulation occurred following weekly administration of eribulin. Finally, the human plasma protein binding of eribulin (100 ng/mL to 1,000 ng/mL) ranged from 46% to 65%.

5.2 Drug-drug interactions

During drug development, Eisai determined that eribulin is a substrate of CYP3A4; however, CYP3A4 has negligible effects on the metabolism of eribulin. Eribulin is a weak inhibitor of P-gp.

Additionally, Eisai submitted the results of study E7389-E044-109 (Study 109) entitled “An Open-Label, Phase I Study to Evaluate the Pharmacokinetics and Tolerance of Co-administration of Oral Multiple Doses of Ketoconazole and an IV (bolus) Infusion of Eribulin in Patients with Advanced Solid Tumors” as an assessment of drug-drug interactions. This drug-drug interaction study demonstrated that the AUC of eribulin was similar whether or not ketoconazole, a strong CYP3A4 inhibitor, was administered to patients.

5.3 Pathway of elimination

The Applicant conducted a mass balance study [E7389-E044-103 or (Study 103)] to determine the major route of eribulin elimination. In this study, six patients received a radiolabeled fixed dose of 2 mg of eribulin. Eribulin was primarily excreted unchanged through the fecal route of elimination (82%). Approximately 9% was excreted through the kidneys and the remainder was metabolized. Additionally, a non-clinical study in rats showed that biliary excretion was likely to be important in the elimination of eribulin.

5.4 Evaluation of intrinsic factors potentially affecting elimination

Eisai conducted a dedicated hepatic impairment study in patients with Child’s A (mild hepatic impairment) and B (moderate hepatic impairment) cirrhosis. The Applicant proposed an initial dose reduction of 0.7 mg/m² in patients with moderate hepatic impairment. Based on the clinical pharmacology assessment, hepatic impairment resulted in decreased clearance of eribulin, prolongation of the elimination half-life, increased AUC, and increased C_{max}. The clinical pharmacology review staff found that the geometric mean dose normalized AUC increased 1.7-fold in patients with mild hepatic impairment and the probability of Grade 4 neutropenia increased with increasing AST despite similar exposure. Based on these data, clinical pharmacology review staff and the review team as a whole recommended an initial starting dose of 1.1 mg/m² for patients with mild hepatic impairment.

Based on population PK trends (a 2-fold increase in the geometric mean dose-normalized AUC for patients with moderate renal impairment) between creatinine clearance and eribulin clearance, clinical pharmacology review staff recommended an initial eribulin starting dose of 1.1 mg/m² for patients with moderate renal impairment. Additionally, clinical pharmacology review staff recommended a post-marketing requirement to assess the effects of severe renal impairment on the pharmacokinetics of eribulin.

5.5 Demographic interactions/special populations

OCP review staff analyzed the population PK database submitted by Eisai and found no significant interactions between age, gender, race, and pharmacokinetics. The Applicant did not include data from pediatric patients in this NDA.

5.6 Thorough QT study or other QT assessment

Study E7389-E044-110 (Study 110) entitled “An Open-Label, Multicenter, Single Arm QT Interval Prolongation Study of Eribulin Mesylate (E7389) in Patients with Advanced Solid Tumors” was submitted for review by Eisai and was analyzed by clinical pharmacology reviewers and the QT-IRT. Patients in Study 110 received an eribulin dose of 1.4 mg/m² on days 1 and 8 of a 21-day cycle. A supra-therapeutic dose was not studied. EKG’s in triplicate were obtained prior to the infusions and at the end of the infusion on days 1 and 8 of cycle 1 at multiple time-points prior to the collection of PK data. Additionally, patients wore Holter recorders during the study.

During Study 110, a total of 26 patients were enrolled and received study treatment with 24 patients completing the first cycle. The primary endpoint analyzed by the QT-IRT was the largest mean difference between the time matched baseline QTcF to post-dosing QTcF, considering post-treatment assessments on day 1 and day 8. During the review, QT-IRT review staff described a delayed QTc interval prolongation in the dedicated QT study. The largest upper bound of the 2-sided 90% CI for the change from baseline in QTcF was 18 ms observed by the QT-IRT on day 8. No specific concentration-QT relationship was observed.

Based on the findings in Study 110, QT-IRT members recommended adding a warning to the label that eribulin causes QT prolongation on day 8.

6. Clinical Microbiology

This section is not relevant for this chemotherapy drug. Quality microbiology issues are described in Section 3 above.

7. Clinical/Statistical- Efficacy

The clinical reviewer recommended approval of eribulin mesylate based upon the efficacy and safety results of Study 305. The statistical reviewer stated that the study results supported the claims for the primary endpoint; however, the decision regarding approvability based on the treatment effect size was deferred to the clinical review team.

7.1 Background of clinical program

Refer to Section 2 above that describes the background of the clinical program.

7.2 Design of efficacy studies

This NDA was primarily based on the results of a single randomized controlled trial with supportive evidence from two single-arm phase 2 studies (refer to clinical review for analyses of the two phase 2 studies). The primary study supporting the NDA is Study E7389-G000-305 (Study 305) entitled:

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 Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane.

Study 305 was a randomized (2:1), multicenter, international, open-label, active controlled study comparing eribulin to a single-agent chemotherapy regimen chosen by the investigator. The single-agent chemotherapy regimen was chosen prior to randomization to minimize bias.

Control Arm

The control arm used in Study 305 complicated the analysis of efficacy and safety because the true treatment effects could not be determined without a placebo. Nevertheless, it would be considered unethical or not feasible to randomize patients with metastatic breast cancer to no treatment. No physicians or patients chose best supportive care in the control arm, even though this was an option. Without the consideration of a placebo, the choice for a control arm in a head-to-head trial is whether to use one specific chemotherapy regimen or the “physician’s choice” design used in Study 305.

The specific cancer setting in which a clinical trial will be conducted is an important consideration in the choice of an active control arm. In settings where there is a well-recognized standard of care (i.e., first line therapy of Hodgkin’s lymphoma), the clear choice is to compare the experimental regimen to the standard of care regimen (often this would be an add-on design). In settings such as $\geq 3^{\text{rd}}$ line metastatic breast cancer (or especially in settings without clear effective therapy), where patients have been previously treated with multiple different drugs, there is reasonable justification for use of a “physician’s choice” control arm. Theoretically, both designs might be subject to bias (either by enrolling patients less likely to respond to the single drug control arm versus choosing a potentially less effective therapy in a physician’s choice setting). Requiring physicians to choose the control therapy prior to randomization helps mitigate this bias. Additionally, physicians should be expected to choose a regimen for their patient that would pose a favorable risk-benefit ratio.

In summary, despite the potential disadvantages of bias and increased complexities of data analysis posed by the “physicians choice” design, the control arm chosen for Study 305 was acceptable for the following reasons: inability to enroll patients in a true placebo-controlled trial; lack of an established standard of care in the $\geq 3^{\text{rd}}$ line metastatic breast cancer setting;

overall survival endpoint; and the potential advantage of choosing an individualized regimen with a reasonable risk-benefit profile for each patient that simulates a “real-world” situation. Study 305 could not definitively prove that eribulin is better than placebo (there is the theoretical chance that therapies in the control arm could have increased toxicity with no benefit); however the study could demonstrate improved survival compared to therapies that are commonly prescribed in this setting; this improvement in OS can be considered a real benefit to patients with metastatic breast cancer in the third-line (or greater) setting.

Eligibility Criteria

Patients \geq 18 years-of-age were eligible if they had recurrent or metastatic cancer of the breast; received a prior taxane and anthracycline (unless contraindicated for these regimens); and received a minimum of two chemotherapy regimens for locally recurrent or metastatic disease (a maximum of five prior regimens were allowed). The study allowed but did not require prior therapy with trastuzumab or hormonal therapy. Patients were excluded with inadequate bone marrow function (refer to clinical review for criteria), brain metastases, meningeal carcinomatosis, pregnancy, severe or uncontrolled intercurrent illness, and severe neuropathy at baseline. The eligibility criteria were reasonable; however there was some concern that HER2 positive patients were not required to receive anti-HER2 therapy (see below and clinical review).

General Study Design/Treatment Plan

The study randomized (2:1) patients to receive eribulin (1.4 mg/m² IV over 2-5 minutes on days 1 and 8 every 21 days) or a single agent chemotherapy, hormonal therapy, biological therapy, or best supportive care chosen by the treating physician prior to randomization. The protocol specified dose modification guidelines for eribulin for hematological and other toxicities. Dose modifications for control arm treatments were to be made according to product labeling. The protocol required tumor assessments every 8 weeks for progression and response, irrespective of study arm assignment. Additionally, investigators continued to follow patients every three months for overall survival, the primary endpoint.

Statistical Design

Patients were randomized (2:1) and stratified based on geographical region, HER2/neu status, and prior treatment with capecitabine. The statistical analysis plan included the following sample size considerations: one interim analysis after 50% of events; median expected OS of 9 months in the TPC arm and an expected HR of 0.75; 5% alpha (two-sided); and 80% power to detect the HR of 0.75. Based on the assumptions, the required number of events (deaths) for the final analysis was 411.

As previously stated, the primary endpoint was OS (stratified log-rank test). PFS based on independent review was also to be tested using a 2-sided log rank test if OS was positive. Tumor response rates with 2-sided 95% CI's were to be estimated using Fisher's exact test. There was no plan to control the overall false positive rate for the secondary endpoints specified.

7.3 Study results

Summary

The efficacy of eribulin was primarily based on the results of Study 305, a study that demonstrated a statistically significant improvement in overall survival compared to the control “physician’s choice” arm. The major issue regarding the consideration of efficacy for this application was whether FDA could rely on the results of a single study to support the approval of eribulin. The FDA guidance document “*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*” describes the situations in which FDA can rely on a single study plus additional supportive data.

Study 305 was a large (n=762), multi-center study in which no single study site provided an unusually large fraction of the patients. In general, there was consistency across most subsets as to the direction of the HR (point-estimates) favoring eribulin. A specific alpha allocation plan was not provided for secondary endpoints; however, there was a nominally statistically significant result for an improved objective response rate for eribulin compared to the control arm [11.2% versus 3.9% (p = 0.0006)]. PFS was not statistically significantly improved according to the Independent Review. The p-value for the investigator analysis of PFS was markedly lower than the IRC analysis; however the difference in median PFS for the two estimates were similar [indicating that investigators likely called progression events earlier in *both* arms]. The results of the primary analysis of OS were not necessarily statistically persuasive [HR 0.81 (95% CI: 0.660 to 0.991); p = 0.041]; however, the results of the updated OS analysis after approximately 75% of events occurred appeared more favorable for OS with limited loss of follow-up [HR 0.81 (p = 0.014)]. Finally, the guidance document states that “reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.” Study 305 demonstrated an improvement in OS. In a heavily pre-treated population of patients with metastatic breast cancer, it is unlikely that patients would elect to be randomized to a treatment with inferior survival.

However, because Study 305 was a single study with a complex control arm in a highly refractory population, it cannot be determined if eribulin would be superior to currently used drugs in earlier stages of breast cancer. Thus, the review team recommended limiting the indication to patients who have received an anthracycline, a taxane and at least two chemotherapy regimens in the metastatic setting.

Demographics of Study 305

Baseline demographic variables were well-balanced between treatment arms. Most patients (92%) were White and most (76%) were post-menopausal. A total of 19% of patients were enrolled in the U.S.; however, 64% were enrolled in North America, Western Europe, or Australia. A total of 67% of patients were ER positive and 16% were HER2-receptor positive. A total of 19% of patients were “triple negative” for ER, PR, and HER2. The median number of prior chemotherapy regimens was four and 83% of HER2+ patients received HER2+ therapy with trastuzumab or lapatinib prior to enrollment.

Consideration of Choice of TPC Therapy

To reduce bias, the protocol required investigators to choose control therapy prior to randomization. No patient chose best supportive care as a treatment option. Vinorelbine, gemcitabine, and capecitabine were the most common single-agent regimens chosen for patients in the TPC arm. Table 3, copied from the statistical review, shows the distribution of therapies that patients received in the control and eribulin arms.

Table 3: Therapies Assigned and Administered to Patients in the Control (TPC) Arm

Treatment	Assigned n (%)	Actual n (%)
Eribulin	508 (100.0)	503 (99.0)
TPC: Vinorelbine	65 (25.6)	61 (24.0)
TPC: Gemcitabine	46 (18.1)	46 (18.1)
TPC: Capecitabine	45 (17.8)	44 (17.3)
TPC: Taxanes	41 (16.1)	38 (16.1)
TPC: Anthracyclines	24 (9.4)	24 (9.4)
TPC: Hormone therapy	8 (3.1)	9 (3.5)
TPC: Others	25 (9.8)	25 (9.8)

Analysis of the Primary Endpoint

As previously stated, the primary endpoint was overall survival. The final analysis was conducted for OS using a two-sided stratified (by HER2 status, prior capecitabine, and geographic region) log-rank test. Follow-up for OS was acceptable with only 0.8% of patients considered lost to follow-up at the time of data cut-off. Table 4, copied from the statistical review, shows the overall survival results for Study 305. Median OS was improved by 2.5 months compared to therapies administered to patients in the active control arm.

Table 4: OS Analysis (ITT population)

Overall Survival	Eribulin (n=508)	Control Arm (n=254)
Number of deaths (%)	274 (54)	148 (58)
Median, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
Hazard Ratio (95% CI) ^a	0.81 (0.66, 0.99)	
p-value ^b	0.041	

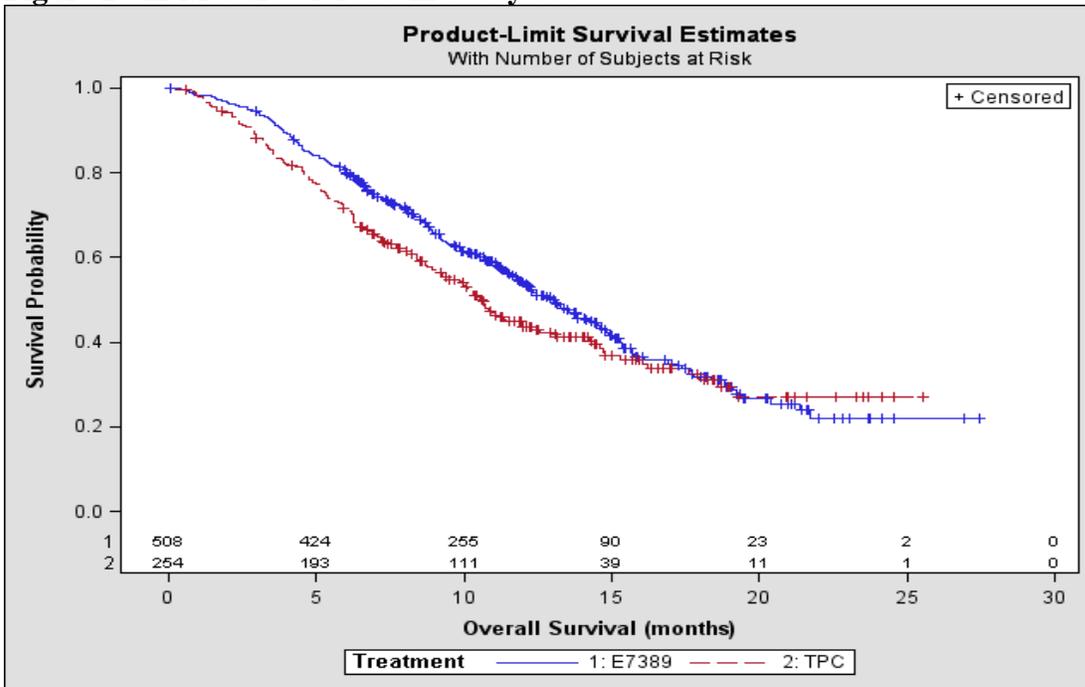
Abbreviations: CI, confidence interval

^a Based on a Cox proportional hazards model stratified by geographic region, HER2 status, and prior capecitabine therapy.

^b Based on a log-rank test stratified by geographic region, HER2 status, and prior capecitabine therapy.

Figure 2, copied from the statistical review, shows the Kaplan-Meier Curves for the two treatment arms in Study 305. In the updated analysis described below, the curves no longer cross. Note that the number of patients at risk is low when the two curves cross.

Figure 2: K-M Curve for OS in Study 305



An updated analysis confirmed the sustained effect on OS (Table 5 and Figure 3, copied from the FDA statistical review). The p-value was lower (0.014) based upon the updated data although the overall HR was similar. Because of the lack of alpha allocation for this analysis and because a statistically significant result was not obtained for the primary PFS analysis (based on the IRC), this reviewer recommends against inclusion of the updated p-value in the label because the p-value cannot be properly interpreted.

Table 5: Updated OS Results (ITT) Population

Overall Survival	Eribulin N = 508	TPC N = 254
Number of Deaths (%)	386 (76.0%)	203 (79.9%)
Median Survival – months (95% CI)	13.2 (12.1, 14.3)	10.5 (9.2, 12.0)
p-value	0.014	
HR	0.81 (0.68, 0.96)	

that the overall treatment effect was not primarily based upon the inclusion of patients in the control arm who repeated a prior therapy

8. Safety

8.1 Adequacy of database, major safety findings

Overall, safety was demonstrated in the primary pivotal study (Study 305) through a statistically significant improvement in overall survival compared to the control group. The clinical reviewer analyzed data from a total of 1,222 eribulin-treated patients; however, she conducted the primary analysis of safety using data from Study 305 in which a total of 503 patients received eribulin. Given that the proposed indication is for the treatment of patients with metastatic breast cancer who have received previous anthracycline and taxane therapy, and given the improvement in overall survival, the size of the safety database appeared adequate.

The decision regarding attribution of specific adverse reactions to eribulin was complicated during this NDA review because the control arm used in Study 305 (and the single-arm nature of the other studies submitted to the database) consisted of multiple different chemotherapy drugs. This design facilitated a “real-world” analysis of whether eribulin prolongs overall survival compared to single-agent regimens commonly used to treat breast cancer; however, attribution of specific events required a careful analysis of the data and in some cases, clinical judgment. For example, the overall incidence of diarrhea was identical in patients treated with eribulin and TPC (18%). If a hypothetical adverse event occurred at the same rate in an experimental arm compared to a placebo, the adverse event (i.e., diarrhea) would likely be excluded from product labeling; however, (for eribulin) because diarrhea commonly occurs following chemotherapy, it was determined by clinical review staff that diarrhea is likely an adverse reaction (AR) attributable to eribulin.

In the 305 study, a total of 503 patients received eribulin compared to 247 in the control group. The most common therapies administered to patients in the control group included vinorelbine 25%, gemcitabine 19%, capecitabine 18%, taxanes 15%, and anthracyclines 10%. A total of 3% of patients received hormonal therapy.

The major safety findings during the review of this application were related to neutropenia and peripheral neuropathy. Common adverse reactions included neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The label includes instructions on the monitoring and management of patients with neutropenia as neutropenia increases the risk for severe and fatal infections.

8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests

Deaths

The analysis of overall survival favored treatment in the eribulin arm. As described in the clinical review, a total of 53.9% of patients in the eribulin arm and 57.9% of patients in the control arm died at the time of data cut-off. A high proportion of patients were expected to die

on study because the study population consisted of patients with metastatic (i.e., incurable) breast cancer who had received at least two prior treatment regimens in the metastatic setting. In some cases, attribution of deaths to progressive disease or toxicity due to treatment was difficult.

According to the investigators' assessments, 3% of patients in both arms died due to a reason other than disease progression. More patients died within 30 days of the last dose of study drug in the control arm compared to the eribulin arm (7.7% versus 4.0%, respectively). Thus, eribulin appears to demonstrate a relatively favorable safety profile compared to other drugs used to treat metastatic breast cancer (with the understanding that cytotoxic chemotherapy can cause severe toxicities in patients with cancer and that oncologists are trained to manage such toxicities and adequately consent patients).

Among eribulin-treated patients, up to four died of infections within 30 days of the last dose of study drug (two with antecedent neutropenia, one with antecedent mucositis, and one in the setting of disease progression and diabetes considered unrelated to eribulin by the Applicant). Infection caused up to 3 deaths in the control arm including one case of invasive aspergillosis in a patient receiving taxane therapy. Most deaths within 30 days of the last dose of eribulin were considered related to disease progression. One patient with a history of diabetes and diabetic retinopathy died of diabetic ketoacidosis

SAEs

A similar number of patients in both treatment groups experienced an SAE (25 % and 26% in the eribulin and control groups, respectively). The largest difference between treatment groups according to MedDRA SOC (system-organ-class) hierarchy was in the "blood and lymphatic system disorders" SOC [6% versus 2% (per-patient incidence rate)]. No other SOC category differed by more than 1% between groups (except for "respiratory disorders" and "general disorders" with higher incidence rates in the control groups).

The only preferred terms (SAE analysis) with a 2% or higher incidence rate in the eribulin arm compared to the control arm were febrile neutropenia and neutropenia. Finally, the per-patient incidence rate of SAEs in Study 305 was similar to the pooled per-patient incidence rate of SAEs in all patients who received eribulin.

Drop-outs and Discontinuations due to Adverse Events

According to the clinical reviewer's analysis of the safety data, a total of 78% of eribulin-treated patients discontinued eribulin due to progressive disease or clinical progression compared to 75% in the control group. Also, a total of 11% of eribulin-treated patients discontinued therapy due to an adverse event compared to 10% in the control group. The most common adverse event leading to discontinuation of therapy in the eribulin arm was neurotoxicity (6% of patients). Six patients (1%) discontinued due to infections, 5 patients (1%) discontinued due to asthenia/fatigue, and three patients (1%) discontinued due to elevations in liver enzymes. In addition to the patients who discontinued eribulin due to an adverse event, there were seven patients who discontinued for a reason assigned as other, physician decision, or subject withdrawal who likely withdrew due to an adverse event. Two

of these patients experienced moderate or severe neuropathy and two patients discontinued eribulin in the setting of an infection or an infection related complication.

Common Adverse Events

The clinical reviewer conducted a review of all adverse events and severe adverse events using the structure of the MedDRA hierarchy. Common adverse events occurring in at least 10% of the Study 305 eribulin-treated population included bone marrow suppression (neutropenia, leucopenia, anemia), alopecia, gastrointestinal events (nausea, diarrhea, vomiting, constipation, nausea), constitutional events (fatigue/asthenia, anorexia, weight loss, fever), pain-related events (headache, back pain, bone pain, arthralgia, myalgia, extremity pain), respiratory events (dyspnea, cough), and neurologic events (paresthesia, peripheral sensory neuropathy). Labeling used composite terms for asthenia/fatigue and peripheral neuropathy rather than the preferred term. The use of these composite terms was considered acceptable by the review team; however, the clinical reviewer recommended the inclusion of additional preferred terms to the peripheral neuropathy term. Refer to the clinical review for a full discussion of all events considered during the review for product labeling.

The most common severe AEs (listed as severe in the CRF or \geq Grade 3) in eribulin-treated patients were neutropenia [57% (based on laboratory test values)]; leucopenia (14%); and febrile neutropenia (5%).

Laboratory Tests

As expected from the review of adverse events, neutropenia commonly occurred in patients receiving eribulin. As described in the clinical review, a total of 29% of patients in the eribulin-treated group experienced Grade 4 neutropenia as described in laboratory datasets. For patients who experienced Grade 4 neutropenia, the mean time to recovery to greater than 500 neutrophils per microliter was 8 days. Thrombocytopenia occurred less commonly than neutropenia. Five eribulin-treated patients experienced \geq Grade 3 thrombocytopenia and two patients experienced Grade 4 thrombocytopenia.

Due to competing factors related to the presence of hepatic metastases in the breast cancer population, it was difficult to assess the relationship of eribulin and liver injury. Nevertheless, ALT elevations occurred more commonly among patients treated with eribulin compared to patients in the control group. Among patients with Grade 0 or 1 ALT levels at baseline, 18% of eribulin-treated patients experienced Grade 2 or greater ALT elevations, compared to 12% of patients in the control group. No deaths due to liver failure were described. One patient without documented liver metastases transiently met the criteria for Hy's law; however, the abnormalities resolved despite re-treatment with eribulin.

8.3 Immunogenicity

Issues regarding immunogenicity are not applicable to this small molecule drug.

8.4 Special safety concerns

The clinical reviewer identified neuropathy as a submission-specific safety concern. Vinca alkaloids and taxanes (both also inhibit microtubules) also cause neuropathy. Neuropathy was the most common reason for drug discontinuation. Some patients experienced prolonged

neuropathy following eribulin treatment (5% of patients experienced neuropathy greater than one year). The review team recommended that neuropathy be included in the Warnings section of product labeling.

8.5 Discussion of primary reviewer's comments and conclusions

The primary reviewer considered the safety profile of eribulin to be acceptable for the indicated population based on the finding of an improvement in overall survival compared to the control arm. Overall, the adverse reaction profile of eribulin was similar in nature to those observed with other microtubule-inhibiting drugs including vinca alkaloids. Additionally, a lower percentage of patients died within 30 days of the last dose of study drug in the eribulin arm compared to the control arm.

8.6 Highlight differences between CDTL and review team with explanation for CDTL's conclusion and ways that the disagreements were addressed

There were no major differences between the CDTL and review team regarding this section of the review.

8.7 Discussion of notable safety issues (resolved or outstanding)

The major unresolved safety issue involves a PMR related to the safe use of eribulin in patients with severe renal failure.

9. Advisory Committee Meeting

An advisory committee meeting was not held for eribulin. This decision was agreed upon by the clinical and statistical review team and division/office management. The primary justification for this decision relates to the primary endpoint of Study 305. A statistically significant improvement in overall survival is considered the "gold standard" for the approval of oncology drugs. In lieu of an advisory committee, this application was discussed separately with three SGEs including a patient representative and a breast cancer expert. The three SGEs supported the FDA decision to approve eribulin based on the briefing document submitted to the SGEs.

10. Pediatrics

Eisai requested a disease-specific waiver for pediatric patients (0-18 years) based on the intended indication of breast cancer because breast cancer rarely occurs in the pediatric population. Thus, studies in children would be impossible or highly impractical to conduct because the patient population is too small. PeRC held a meeting on 5/5/2010 to discuss the PREA waiver requirement for eribulin. PeRC notified the Division by email regarding the decision to grant the waiver on May 18, 2010.

Additionally, Eisai agreed to participate in a discussion of potential applications for eribulin in pediatric cancers at a meeting of the Pediatric Subcommittee of the Oncology Drugs Advisory Committee scheduled during the fourth quarter of 2010. Conduct of a study of eribulin in children that is set forth in a Pediatric Written Request issued by FDA might satisfy the requirements of the Best Pharmaceuticals for Children Act.

11. Other Relevant Regulatory Issues

11.1 Application Integrity Policy (AIP)

Based on the review of the CRFs by the clinical reviewer and DSI audits, the primary data submitted to this application were found to be reliable for the primary analyses of safety and efficacy. The applicant certified that Eisai did not use any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 210532.

11.2 Financial disclosures

As described in the clinical review, Eisai reported no financial conflicts as defined in 21 CFR 54.2(a) (b) and (f).

11.3 GCP issues

The 305 study report contained a statement that the study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice for Trials on Medicinal Products, including archiving of essential study documents. Eisai submitted a total of 17 audit certificates for Study 305.

11.4 DSI audits

The review division and DSI chose five clinical sites for inspection based on the size of the enrolled study population, number of major protocol violations, or high rate of treatment responders. Additionally, DSI inspected the study sponsor, Eisai, and a study CRO. All sites received interim classifications as VAI or voluntary action indicated except for the Bellflower California site (Dr. Han Koh) that was classified as NAI (no action indicated). At each of the sites, the primary efficacy endpoint data were verifiable against source records and there was no evidence of underreporting of AEs. In general, DSI predominately identified deficiencies related to lack of adherence to the protocol in regards to obtaining all required lab tests at each visit and insufficient records regarding infusions. However, the preliminary reports indicated that the primary data were adequate for the overall assessment of safety and efficacy at the five sites.

An inspection of the (b) (4) confirmed that (b) (4) work was verified by the study sponsor. DSI noted deficiencies in regards to failure to meet all terms of the contract including the requirement to visit all sites within 2 weeks of enrollment of the first subject. (b) (4) was unable to bring on more monitors early into the study. By 2009, the CRO became compliant with submission of monitoring reports and subsequently, monitoring and reporting appeared to be in compliance. In their overall assessment, DSI stated that the deficiencies did not appear to have resulted in significant issues with conduct of the study and were unlikely to affect data reliability. Finally according to DSI, no evidence from the inspection of Eisai suggested a lack of reliability of efficacy data or significant underreporting of safety data.

11.5 Other discipline consults

Pediatric and Maternal Health had the following recommendations and conclusions:

- Embryo-fetal toxicity and teratogenicity information should be conveyed in the Pregnancy subsection and the Warnings Section of labeling. Comment: The label was revised to include a Warning for Embryo-Fetal toxicity.
- The pregnancy subsection should include only information about the use of eribulin in pregnancy and this information should be placed in the Warnings Section and the Patient Counseling Information section of labeling. It was DBOP's opinion that there is a special place in the label (i.e., Use in Specific Populations) that is to contain the information regarding use in pregnant women. This information should be contained within this section for consistency and not be included additionally in the Warnings section of the label. The patient counseling section was revised as per the Maternal Health Consult recommendations.

11.6 Other outstanding regulatory issues

Not Applicable.

12. Labeling

12.1 Proprietary name

The proposed proprietary name for eribulin mesylate injection is Halaven (Injection). DMEPA notified DBOP by email on May 14, 2010 that the name Halaven was acceptable from a look-alike and sound-alike perspective. Additionally, no objections to the name Halaven were identified by DDMAC or the clinical review team during the review cycle. The proprietary name was granted in a letter to Eisai dated July 2, 2010.

12.2 Labeling issues raised by DDMAC

The clinical review team and clinical pharmacology reviewers revised labeling to define terms such as mild, moderate, and severe hepatic impairment as recommended by DDMAC.

The clinical review team, however, did not agree with the DDMAC recommendation to limit the indication to patients who experienced disease progression within 6 months of their last chemotherapeutic regimen. The six month stipulation was an inclusion criterion of the study. The following are reasons why this reviewer disagreed with the added stipulation:

- Differences in timing of obtaining imaging in clinical practice compared to a clinical study makes determination of the exact timing of progression difficult.
- There is a lack of a survival benefit for other cytotoxic drugs administered to women with metastatic breast cancer following treatment with taxanes and anthracyclines (and two therapies in the metastatic setting).
- Finally, most women will be expected to progress within six months of their prior regimen. In the 305 study, median estimated PFS for the prior regimen was 3.7 months in the eribulin arm.

12.3 Physician labeling

In general, all sections of the label were revised for brevity and clarity. Command language was preferred as directed by the PLR. The remainder of this section of the review will only focus on high-level issues regarding the label submitted by Eisai. Numbering below is consistent with the applicable sections in product labeling. This review will not comment on all sections (for example, if only minor edits were made to a section). This CDTL agreed with the recommendations made by the review teams that are described below.

1. Indications and Usage

The review team recommended limiting the indication to the population enrolled into Study 305. Specifically, that eribulin should be 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.

The label submitted by Eisai stated that Halaven was indicated for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens. The Applicant's proposed indication statement would allow for (b) (4)

, this CDTL agrees with the review team that the indication should represent the population studied in Study 305.

2. Dosage and Administration

The review team recommended that dosing recommendations for patients with hepatic and renal impairment be described in Section 2.1 (to highlight the importance of these modifications to clinicians).

The dose modification section was reformatted for clarity. The statement that (b) (4) was removed because this statement was not necessary for the safe use of eribulin and could be used promotionally.

4. Contraindications

The Applicant originally proposed to contraindicate (b) (4). This contraindication was not supported by data and at least two patients were re-treated with eribulin after previous hypersensitivity reactions.

5. Warnings and Precautions

The review team proposed two additional Warnings in this section of the label: Embryo-Fetal Toxicity and QT prolongation (see Section 5.6 of the review regarding QT prolongation). The review team disagreed with the Applicant's proposal that the Embryo-Fetal toxicity section be called (b) (4) as it might imply that (b) (4) is considered the adverse event rather than the true concern of Embryo-Fetal Toxicity. Section 11.5 of this review contains a

discussion regarding a separate warning for pregnant women that the MFH team recommended for inclusion in the label.

The (b) (4) warning was changed to a Neutropenia warning to reflect the primary concern with eribulin administration. The review team recommended the inclusion of additional information to indicate that prolonged neutropenia of greater than one week can occur following eribulin treatment and that patients with increased alanine aminotransferase or aspartate aminotransferase levels are at increased risk for neutropenia.

The revised neuropathy warning included specific information characterizing the incidence, duration, and severity of peripheral neuropathies and that some patients experienced neuropathy for longer than one year.

6. Adverse Reactions

The review team added two paragraphs in the Adverse Reactions section. One paragraph further described the scope (incidence and severity) of cytopenias occurring during Study 305. Cytopenias were described using laboratory data rather than investigator derived adverse event descriptions. The second paragraph described frequent liver function test abnormalities that occurred during the conduct of Study 305.

8. Use in Specific Populations

Review staff recommended that this section of the label include data on patients with moderate renal impairment and a lower starting dose based on rich PK sampling from population studies. Additionally, review staff recommended a lower starting dose of 1.1 mg/m² for patients with moderate hepatic impairment (Child-Pugh B).

12. Clinical Pharmacology

This section was revised for clarity and brevity. Additionally, review staff recommended that potentially promotional statements not backed up by clinical evidence should be removed from the label.

14. Clinical Studies Section

Information regarding the objective response rate and duration of response was added to the label. Updated KM curves for OS were included in product labeling without the updated p-value. Review staff recommended against using the specific term (b) (4) as this was considered to be a term of art.

15. Patient Counseling and PPI

The PPI was revised to be consistent with MedGuide format as per the recommendation of DRISK (see Section 12.6 below).

12.4 Major issues not resolved

Not applicable.

12.5 Carton and immediate container labels

On June 14, 2010, FDA communicated requested revisions to the Halaven carton and container labels. Eisai responded with revised carton and container labels on July 23, 2010. Based on the Eisai submission, ONDQA requested an additional edit regarding labeling that was communicated to Eisai by email on July 14, 2010. Negotiations regarding the carton and container labels are ongoing and final agreement on the revised carton and container label has not been made at this time.

12.6 Patient labeling/Medication guide

Patient labeling was not specifically required by FDA for this application for the following reasons:

- Trained oncologists will administer eribulin (who are expected to adequately consent patients regarding the risks and benefits of chemotherapeutic drugs prior to administration).
- Eribulin will be administered by infusion centers and it is not clear that patient labeling will be transmitted by the pharmacist to the patient.

Eisai stated in a June 29, 2010 submission that FDA allowed patient information for injectable oncology drugs including Ixempra and Abraxane and Eisai stated that the PPI could educate patients on the appropriate use of therapy with eribulin. *Comment: Based on prior precedent, DBOP did not object to the PPI even through it was not required (PPIs are not universally included with labeling for other oncology products). As per DRISK recommendations, Eisai revised the PPI so that the PPI would be consistent with MedGuide formatting. The revised PPI was submitted by Eisai on June 29, 2010.*

Following the revised PPI submission by Eisai, the PPI was revised for clarity, brevity, and understandability in conjunction with DRISK and DDMAC recommendations (except for the DDMAC recommendation to further restrict the indication as described above).

13. Recommendations/Risk Benefit Assessment

13.1 Recommended regulatory action

The recommendation of this Cross Discipline Team Leader is for approval of NDA 201532. All review teams recommended approval or reported that there were no findings that would prevent approval. DMEPA determined that the proposed proprietary name of Halaven was acceptable.

13.2 Risk-benefit assessment

As previously stated, the recommendation for approval is based on the results of a single, randomized clinical trial demonstrating a statistically significant survival advantage in patients treated with eribulin compared to a control arm in which therapy was chosen by the patient's physician.

Study 305 was a large (n=762), randomized (2:1), multicenter, international, open-label, active controlled study comparing eribulin to a single-agent chemotherapy regimen chosen by the

investigator. As described in Section 7 of this review, eribulin improved median overall survival by approximately 2.5 months over the control arm [HR = 0.81 (0.66, 0.99); p = 0.041]. The results were supported by an updated analysis of OS.

Eribulin causes adverse reactions including neutropenia, QTc prolongation, LFT abnormalities, and neuropathy. In some cases, neutropenia can increase the risk for severe or life threatening infections; however, because overall, patients lived longer following eribulin treatment, these risks are acceptable in relationship to the benefits of eribulin for the intended treatment population.

13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies

Eribulin is indicated for the treatment of patients with life-threatening cancer and has demonstrated an overall survival advantage. As such, additional post-market risk management activities are not necessary at this time (other than those required for all NDAs such as those described in 21 CFR 314.81). The proposed USPI contains patient counseling information for trained prescribing physicians.

13.4 Recommendation for other postmarketing requirements and commitments

The following postmarketing requirements (PMRs) and postmarketing commitments (PMCs) have been proposed by the review team and have been discussed with the Applicant. The exact language of the PMRs is pending final sign-off at the Division, Office, and OND levels.

The following PMR (#1) is the sole PMR identified during the review cycle. Clinical pharmacology review staff recommended this PMR because moderate renal impairment increased the mean geometric systemic exposure by approximately two-fold (based on available data from rich PK sampling and not on a dedicated renal impairment study); and, data were not sufficient to assess the effect of severe renal impairment on the pharmacokinetics of eribulin. A dedicated PK study in patients with severe renal impairment is necessary to ensure the safe use of eribulin in patients with severe renal impairment.

Because eribulin improved the overall survival of the intended population, FDA review staff determined that this requirement is an appropriate post-approval requirement (and should not be required prior to the approval of eribulin).

1. To conduct a dedicated clinical trial assessing the safety and pharmacokinetics of Halaven, 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 trial design should include subjects with normal renal function and subjects with severe renal impairment.

The study population may include patients with advanced or metastatic solid tumors that are no longer responding to available therapy, i.e., similar eligibility criteria with regard to cancer type as for Trial 108 conducted in cancer patients with hepatic impairment. The renal function subgroups should have similar demographic characteristics with respect to

age, gender and weight. The number of patients enrolled in the trial should be sufficient to detect clinically important PK differences that would warrant dosage adjustment recommendation. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan should be included in the final protocol submitted to FDA.

The timetable you submitted on September 30, 2010 states that you will conduct this trial according to the following schedule:

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

The following PMC (#2) was agreed upon by the applicant and will provide confirmatory information regarding the overall effectiveness of eribulin in patients with metastatic breast cancer previously treated with at least two chemotherapy regimens in the metastatic setting (including an anthracycline and a taxane).

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

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

The timetable you submitted on September 30, 2010 states that you will conduct the trial according to the following schedule:

Final Report Submission: March 1, 2013.

The following PMC (#3) was agreed upon to allow for an additional assessment of outcomes in a patient population that differs from the population enrolled into E7389-G000-305. The population in study E7389-G000-301 will be capecitabine naïve and less heavily pretreated. Additionally, the study will provide additional data on patients who progress while on treatment with a taxane.

3. To submit a final study report for ongoing trial E7389-G000-301, "A Phase III Open Label, Randomized Two-Parallel-Arm Multicenter Study of E7389 versus Capecitabine in Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes." This study report will include a subset analysis of overall

survival in patients that progressed while on treatment with a taxane or other microtubule inhibiting agent. The original protocol for clinical trial E7389-G000-301 was submitted to FDA on November 17, 2005, and began patient accrual on September 20, 2006. We also acknowledge receipt of the protocol amendments received on December 14, 2005; March 2, 2006; May 11, 2006; December 5, 2006; October 31, 2007; March 6, 2008; and March 3, 2009.

The timetable you submitted on September 30, 2010 states that you will conduct the trial according to the following schedule:

Trial Completion Date: March 2012
Final Report Submission: February 2013.

ONDQA review staff recommended PMC (#4) to allow for improved product quality by allowing the DS and DP to be accurately identified.

4. To provide a single Prior Approval Chemistry, Manufacturing and Controls (CMC) supplement containing all of the following data and information:
 - Synthesis of the enantiomers of starting materials (b) (4); and analytical methods and acceptance criteria, with appropriate justification, specific to each enantiomer.
 - Analytical methods and acceptance criteria with appropriate justification for Other Specified, Unspecified and Total Impurities in starting material (b) (4) and revised intermediates (b) (4)
 - An identification test for intermediate (b) (4)
 - Results of the evaluation for specificity of the current identification method for (b) (4) and, if necessary, develop a more selective method.
 - More selective methods for identification and purity for the diastereomers of starting material (b) (4)

The timetable you submitted in the amendment dated September 17, 2010 states that you will submit the supplement according to the following schedule:

Final Report Submission: March 31, 2011

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

/s/

STEVEN J LEMERY
11/09/2010