CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201532

SUMMARY REVIEW

Office Director Summary Review for Regulatory Action

Date	November 12, 2010
From	Richard Pazdur, MD
Subject	Office Director Summary Review
NDA #	201532
Applicant Name	Eisai, Inc.
Date of Submission	March 30, 2010
PDUFA Goal Date	December 30, 2010
Proprietary Name / Established (USAN) Name	Halaven Injection eribulin mesylate
Dosage Forms / Strength	Injection in vials/1mg/2mL
Proposed Indication(s)	For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Regulatory Project Manager	Vaishali Jarral
Medical Officer Review	Martha Donoghue
Statistical Review	Weishi Yuan
Pharmacology Toxicology Review	Lori Kotch
CMC Review/OBP Review	Josephine Jee & Ying Wang
Microbiology Review	Robert Mello
Clinical Pharmacology Review	Stacy Shord
DDMAC	Carole Broadnax & Cynthia Collins
DSI	Lauren Iacono-Connors
CDTL Review	Steven Lemery
OSE/DMEPA Consult	Loretta Holmes
OSE/DRISK Consult	Robin Duer
Maternal Health Team Consult	Jeanine Best

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
DDMAC=Division of Drug Marketing, Advertising and Communication
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

1. Introduction/Background

Halaven Injection (eribulin mesylate) is a new chemical entity that inhibits tubulin polymerization and microtubule dynamics (i.e., inhibition of microtubule growth but not shortening), interfering with normal mitotic spindle formation resulting in blocks within the prometaphase portion of mitosis.

Eisai, Inc. sought regular approval for Halaven Injection (eribulin mesylate) for (b) (4) with metastatic breast cancer based on demonstration of a statistically significant and clinically meaningful improvement in overall survival (OS) in a single trial. The effect on OS was confirmed by an updated analysis showing the treatment effect to be persistent and statistically robust. The effect was consistent across relevant subgroups and supported by evidence of anti-tumor activity with improvement in progression-free survival

(PFS) and durable objective tumor responses in the major efficacy study and in two supportive studies. The toxicity profile of eribulin is similar to that observed with other microtubule-inhibiting agents; the major toxicities are transient, reversible myelotoxicity and monitorable peripheral neuropathy.

2. Clinical/Statistical-Efficacy

Data from study 305 serves as the primary basis for the efficacy evaluation. The supportive evidence of efficacy is provided in the integrated summary of efficacy based upon pooled data from studies 305, 201, and 211. Only data from subjects who were treated with the same dose and schedule of eribulin proposed in the product label were used in the integrated efficacy analysis.

This NDA is primarily supported by a single, multicenter trial from the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) trial (protocol E7389-G000-305), entitled "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 primary objective of the study was to compare the OS of eribulin-treated patients with the OS of patients treated with treatment of physician's choice (TPC). Secondary efficacy objectives included PFS, objective tumor response rate (ORR), and duration of response.

Statistical Analysis Plan:

The original statistical analysis plan specified a sample size of 630 patients and a plan to conduct an interim analysis for efficacy or futility after 206 events (50% of the final events) and a final analysis of OS after 411 events (deaths). The analysis plan was revised after an interim assessment revealed that the event rate was smaller than expected; the amendment resulted in an increase in sample size from 630 to 1000 patients. In the final analysis plan, the nominal significance level for the interim test was 0.003, and the nominal level of significance for the final analysis was 0.049, based upon the O'Brien and Fleming alpha spending function. The study was to be terminated for efficacy ($p<0.003$) or futility (if the interim analysis demonstrated a hazard ratio in which the lower limit of the 95% confidence interval for the hazard ratio of OS higher than 0.85).

RESULTS

Study 305 enrolled a total of 762 patients with locally recurrent or metastatic breast cancer who had received two to five prior chemotherapy regimens, including an anthracycline and a taxane. The Data Monitoring Committee (DMC) recommended termination of the trial after the final analysis of OS.

Ninety-one percent of patients in Protocol 305 had an ECOG performance status of 0 or 1 at study entry. Tumor prognostic characteristics were similar between arms. The study population consisted of 67% ER+ patients, 49% PR+ patients, 74% HER2/*neu*- with 19% of the population having triple negative (ER^-, PR^-, HER2/*neu*-) disease. The majority of patients (82%) had visceral disease, with 60% having hepatic metastases and 38% pulmonary metastases, while 61% had osseous metastases. Approximately half the patients had three or more sites of metastatic disease. The median number of prior chemotherapy regimens was four in each arm.

The final analysis of OS was conducted after 422 events and demonstrated a significant improvement in survival, crossing the pre-specified, adjusted boundary for a significant result of p=0.049, two-sided with a hazard ratio of 0.81[(95% CI: 0.66, 0.99); p=0.041; two-sided stratified log-rank test, stratified by HER2/*neu*

status, prior capecitabine exposure, and geographical region]. The median OS was 2.5 months longer in the eribulin-treated patients than in the control arm (13.1 months vs. 10.6 months).

At FDA's request, the results of an updated, unplanned survival analysis was conducted after 589 deaths and demonstrated that the treatment effect on OS was persistent and consistent with the primary analysis. This updated survival analysis yielded a HR of 0.81 (95% CI 0.68, 0.96), p=0.014, stratified log-rank test) and difference in median survival times of 2.7 months among eribulin-treated patients compared to the control arm. These updated results are below and are also included in product labeling.

Overall Survival in eribulin-treated patients vs. Control Arm - Study 305

Overall Survival	Eribulin mesylate (n=508)	Control Arm (n=254)
Primary survival analysis		
Number of deaths	274	148
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	
Updated survival analysis		
Number of deaths	386	203
Median, months (95% CI)	13.2 (12.1, 14.4)	10.6 (9.2, 12.0)

CI = confidence interval

[a] Based on 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.

Secondary Efficacy Endpoints

Results from protocol 305 showed a statistically higher ORR for patients in the eribulin arm compared to TPC (11.2% vs. 3.9%, p=0.0006) based on independent review-determined response rates. Among responding patients in the eribulin arm, the median duration of response was 4.2 months (95% CI: 3.8, 5.0 months). These findings confirmed and were consistent with, the ORR determine by the clinical investigators. PFS as determined by independent review was not statistically significantly prolonged but favored the eribulin arm [HR 0.87 (95% CI: 0.71, 1.05), p=0.14] with median PFS times of 113 days in the eribulin arm and 68 days in the TPC arm. This finding is consistent with the significant improvement in PFS based on investigator-determined disease progression [HR 0.76 (95% CI: 0.64, 0.90), p=0.002], with median PFS times of 110 days and 66 days in the eribulin and TPC arms, respectively.

Supportive studies

The application also contained the results from two single-arm trials in patients with relapsed or refractory metastatic breast cancer (Protocols 201 and 211). These studies were originally intended to support a request for accelerated approval, based on demonstration of durable objective responses (primary endpoint) in patients who had previously received an anthracycline and a taxane; therefore the primary analysis of response rates was based on independent reviewer assessment. Overall response determined by independent review were 11.5% (95% CI: 5.7%, 20.1%) and 9.3% (05% CI: 6.1%, 13.4%) with median durations of response of 171 and 126 days, in Protocols 201 and 211, respectively.

3. Safety

The safety database for eribulin mesylate was adequate to characterize the safety of this product for the proposed indication. Eribulin has been administered to 1,222 patients in open-label and active-controlled trials enrolling patients with various primary tumors; within the safety experience, there was safety data for 240 patients who received eribulin at least 6 months. The safety profile reported in the overall safety database was similar to that reported in eribulin-treated patients enrolled in Protocol 305. Since Protocol 305 was the largest completed clinical trial with an internal control, the adverse reactions for Halaven are best characterized in this study.

The most common adverse reactions (≥25%) reported in the 503 eribulin-treated patients enrolled on Protocol 305 were asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy, nausea, and constipation. The most serious adverse reactions were febrile neutropenia (4%) and neutropenia (2%). The incidence of serious adverse events were similar in the two groups (25% in each group) and the proportion of patients who died within 30 days of the last dose of study medication was lower for eribulin-treated patients compared to the control group (4.0 vs. 7.7%). The other major significant toxicity was peripheral neuropathy, which occurred in 36% of eribulin-treated patients and was the most common adverse event resulting in termination of eribulin treatment. In addition, 3% of eribulin-treated patients required dose reductions for peripheral neuropathy. Both sensory and motor neuropathy was reported and neuropathy was persistent (last more than one year) in 5% of eribulin-treated patients. These adverse reactions are appropriately described in product labeling with recommendations for pre-treatment assessment for neuropathy and a complete blood count prior to each dose and recommendations for dose reduction in the event of toxicity.

Moderate increases (NCI CTC grade 2 or higher) in hepatic transaminases occurred in 18% of patients with abnormal liver function tests at study entry; no cases of High's Law were reported. The labeling provides directions for dose reductions in patients who experience significant hepatic dysfunction and recommends lower starting doses for patients with mild (1.1 mg/m^2) or moderate (0.7 mg/m^2) hepatic impairment.

4. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. The microbiological assessment determined that sterility was maintained throughout the manufacturing process. Stability testing supports an expiry of 48 months when stored at 25 °C (77 °F) with excursions permitted to 15° – 30° C (59°-86° F).

5. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the nonclinical pharmacology/toxicology reviewer, Dr. Kotch, and the supervisory reviewers, Drs. Pilaro and Leighton that there are no outstanding clinical pharmacology issues that preclude approval and that no additional pharmacology/toxicology studies are needed.

Specifically, Dr. Kotch concluded that "[T]he nonclinical data used to support this NDA were sufficient to determine the pharmacologic activity of eribulin mesylate, and provided a comprehensive toxicity profile in rats and a partial toxicity profile in dogs. These data also enabled an adequate assessment of genetic and reproductive/developmental toxicity, qualification of drug substance/product and a partial identification of potential clinical toxicities." Further, Dr. Kotch noted that "[B]ased on the levels of impurities that were qualified in the nonclinical testing, Eisai should adjust the acceptance criteria for the drug substance and drug product to levels that do not exceed qualification values."

6. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The major elimination pathway of eribulin in animals and in humans is fecal (82% of the dose in humans) with renal elimination as a minor component (<9%), primarily through excretion of the intact drug. Eribulin is a substrate of P-glycoprotein (Pgp) and weak inhibitor of Pgp. Based on *in vitro* studies, the CYP3A4 enzyme is responsible for eribulin for <1% of hepatic metabolism (<1%) of eribulin. Drug studies showed that eribulin exposure (AUC) is not altered in a clinically meaningful way when co- administered with ketoconazole, a strong CYP3A4 inhibitor. Population PK analyses did not identify any clinically meaningful effects of age, gender and race on the PK profile of eribulin.

The systemic exposure of eribulin was increased in patients with mild and moderate hepatic impairment, which is the basis for the recommended lower starting dose of eribulin of 1.1 mg/m^2 and 0.7 mg/m^2 for patients with mild and moderate hepatic impairment, respectively, in the package insert. Although renal elimination is minor (accounting for elimination of 9% or less of the administered dose), systemic exposure was increased by two-fold in patients with moderate renal impairment which is the basis for the recommended lower starting dose of eribulin of 1.1 mg/m^2 for patients with moderate renal impairment in the package insert and the rationale for the request for a required post-marketing study to further characterize the PK profile of eribulin in patients with severe renal impairment.

The effect of eribulin on the QT interval was assessed and revealed that the maximum mean QTc change from baseline is 11 msec with an upper bound of the 2-sided 90% confidence interval of 18 msec observed on Day 8 of the dosing cycle. The data were interpreted as suggesting a delayed effect of eribulin on QTc interval prolongation; while the magnitude of the delay is small, potential clinical effects cannot be ruled out and therefore this risk has been described in product labeling in the Warnings and Precautions section.

The clinical pharmacology review team concluded that exposure-response (E-R) relationships could not be established for clinical efficacy endpoints due to limited exposure data (n=211 patients) collected as sparse PK samples at the recommended dose and schedule.

Comments cited in the clinical pharmacology review which do not preclude the approval of this application will be conveyed to the applicant in correspondence under the IND. Please refer to Dr. Keegan's Summary review or the clinical pharmacology review for these comments.

7. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding sterility issues that preclude approval.

8. Advisory Committee Meeting

There were no controversial issues identified by the review team or me that would have benefitted from an advisory committee discussion. Three ODAC members were consulted (two physicians and a patient advocate) and considered that the applicant had demonstrated a positive risk:benefit assessment which supported approval for the proposed indication.

9. Pediatrics

The Pediatric Review Committee (PeRC) was conducted on May 5, 2010; the PeRC concurred with the recommendation by the review division that a waiver of the requirements under the Pediatric Research Equity Act as requested by the applicant was appropriate, given the rarity of breast cancer in the pediatric population.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11. Labeling

- *Proprietary name:* I concur with the decision of the DMEPA who determined that the proprietary name of Halaven Injection was acceptable on November 8, 2010.

- *Physician labeling, Carton and immediate container labels, Patient labeling/Medication guide:* All consultant and reviewer recommendations for product labeling were considered in internal labeling discussions, and I concur with the division's recommendations on labeling in consultation with labeling reviewers outside of the division.

12. Decision/Action/Risk Benefit Assessment

- *Regulatory Action:* Approval based on an improvement in OS which provides evidence of efficacy and safety. The indicated population has an unmet medical need, which has already accepted the risks of cytotoxic chemotherapy, as demonstrated by the 2-5 prior chemotherapy regimens administered to patients in the primary efficacy study and their acceptance of alternative chemotherapy regimens in the control arm.

  The demonstration of an effect on survival is considered robust based on the consistency of the finding across relevant subgroups based on patient demographics and tumor prognostic characteristics and the demonstration of statistically significant effects on OS at multiple timepoints (interim analysis, final analysis, and updated analyses). Efficacy is also supported by evidence of anti-tumor activity (improvement in progression-free survival in Protocol 305 and evidence of durable objective tumor responses in Protocols 305, 211, and 201). Furthermore, Dr. Keegan as well as all members of the review team recommended approval of this application.

- *Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies*
  I concur with the recommendation by the division that a REMS is not required for this indication.

- *Recommendation for other Postmarketing Requirements and Commitments*
  Please refer to approval letter.

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/s/

TAMY E KIM
11/12/2010

RICHARD PAZDUR
11/12/2010

Summary Review for Regulatory Action

Date	November 11, 2010
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	201-532
Applicant Name	Eisai, Inc.
Date of Submission	March 30, 2010
PDUFA Goal Date	December 30, 2010
Proprietary Name / Established (USAN) Name	Halaven Injection eribulin mesylate
Dosage Forms / Strength	Injection in vials/1mg/2mL
Proposed Indication(s)	For the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
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DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

Eisai, Inc. submitted an application seeking regular approval for Halaven Injection (eribulin mesylate) for (b) (4) with metastatic breast cancer based on demonstration of a statistically significant and clinically meaningful improvement in overall survival in a single trial. The demonstration of the effect survival at the final analysis was not highly persuasive, however, second study was not required because the effect on overall survival was the effect on survival was consistent observed across relevant subgroups and was also confirmed by an updated analysis showing the treatment effect to be persistent and statistically robust. In addition, the effect on survival was supported by evidence of anti-tumor activity with a statistically significant improvement in overall response rate and a non-significant trend for improvement in progression-free survival as determined by independent review in the major efficacy study and durable objective tumor responses in two supportive studies.

The toxicity profile of eribulin is similar to that observed with other microtubule-inhibiting agents; the major toxicities are transient, reversible myelotoxicity and monitorable peripheral neuropathy.

2. Background

Halaven Injection (eribulin mesylate, also known as E7389) is a new chemical entity that is a macrocyclic ketone analogue of halichondrin B, isolated from the marine sponge *Halichondria okadai*. Eribulin mesylate induces G_2/M cell cycle arrest but does not affect progression through the G1 or S cell cycle phases or the G1/S cell cycle transition point. Eribulin mesylate inhibits tubulin polymerization and microtubule dynamics (i.e., inhibition of microtubule growth, but not shortening), thereby interfering with normal mitotic spindle formation in the prometaphase portion of mitosis.

The initial IND application for this product (IND 64,395) was submitted by the National Cancer Institute in April 2002. A commercial IND (IND 67,193) was submitted on March 31, 2003. Clinical data from both the NCI and the commercial IND were provided in support of this New Drug Application (NDA).

The applicant, Eisai, Inc., met with FDA on September 2, 2005, to discuss the potential for submission of a marketing application for accelerated approval based on demonstration of durable objective tumor responses in patients with breast cancer who had progressed following or were refractory to chemotherapy. The application would be based on the results of two single-arm trials, protocols 201 and 211, with verification of clinical benefit in a randomized study (Study 301) comparing single agent eribulin to capecitabine based on demonstration of a

significant improvement in progression-free survival (PFS) for eribulin-treated patients. The Agency concurred that patients with at least 2 but not more than 4 prior therapies had an unmet medical need, but noted that if another agent were granted regular approval for this population, accelerated approval could not be granted. In addition, the Agency stressed that an objective response rate of 15% might not be sufficient to be considered reasonably likely to predict clinical benefit. For the proposed confirmatory study, FDA stated that a determination of clinical benefit would be dependent upon the magnitude of the treatment effect on PFS (as determined by independent review masked to treatment assignment) and the toxicity profile of the eribulin regimen. FDA stated that the confirmatory trial should have adequate power to detect an effect on overall survival. On February 28, 2006, FDA issued a letter accepting Protocol 301 under a Request for Special Protocol Assessment (SPA). In a subsequent communication on March 7, 2006, FDA provided advice regarding the non-clinical and clinical pharmacology requirements for an NDA.

On April 14, 2006, an End-of-Phase 2 CMC meeting was held, in which FDA stated that the information in the briefing package did not support the suitability of the proposed starting materials. An additional meeting to discuss the acceptability of the proposed starting materials was scheduled for August 7, 2006. This meeting was cancelled based upon receipt of FDA's draft responses on August 3, 2006 and following clarification of those responses in an August 3, 2006 teleconference. In these two communications, FDA again stated that the proposed starting materials were not acceptable and FDA recommended starting materials (b) (4) In the teleconference, FDA further stated that the acceptability of the proposed starting materials will be determined at the time of NDA submission and review. FDA enumerated specific information that would need to be provided in the NDA to support the starting materials.

Eisai requested a meeting, scheduled for January 30, 2007, to discuss the clinical development program and registration strategy for eribulin as a single agent for treatment of metastatic breast cancer that had progressed following standard therapy. The meeting was cancelled upon receipt of FDA's draft responses on January 22, 2007. In their responses, FDA noted HER2-positive patients should have received trastuzumab prior to enrollment into studies of eribulin, that Protocol 305 was not optimally designed due to the heterogeneity of treatment in the comparator arm which might confound assessment of safety and comparative efficacy. FDA recommended that Protocol 301 be used as the primary efficacy study or confirmatory trial in the event of accelerated approval and further recommended that trials supporting regular approval have adequate power (sufficient sample size) to detect an effect on overall survival.

On July 31, 2007, Eisai met with FDA to obtain clarity on FDA's expectations with regard to the independent imaging review for open-label trials (in this case specifically Protocol 211) for determination of tumor-based endpoints in open-label clinical trials.

On Aug 21, 2007, FDA granted eribulin Fast Track designation for the treatment of locally advanced or metastatic breast cancer refractory to or relapsed after treatment with standard therapy based on antitumor activity based on demonstration of antitumor activity.

On August 23, 2007, a pre-NDA meeting was held to discuss a proposed NDA submission seeking accelerated approval based on demonstration of durable objective tumor responses in Protocols 201 and 211. During this meeting agreements were reached regarding the content of an NDA package. However with regard to the acceptability of the NDA package to support accelerated approval, FDA noted that the ORR of (b) (4) appeared low and that adequacy to support approval would be a review issue. FDA also noted that that regular approval of another drug for use in this population would block a subpart H approval for eribulin.

In a teleconference on Dec 14, 2007, FDA informed Eisai that an NDA seeking accelerated approval would no longer be acceptable due to the approval of ixabepilone for this patient population.

On Dec 20, 2007, a teleconference was held to discuss modifications to the analysis plan of Protocol 301, noting that these changes would invalidate the prior SPA agreement. Eisai withdrew the revised protocol and made additional revisions as recommended by FDA, which were accepted as noted in the May 13, 2008 communication from FDA.

On March 21, 2008, a type B meeting was held to discuss the use of the ongoing trial, Protocol 305, to support an NDA. FDA recommended that Eisai complete study 301 before submitting the NDA due to the following concerns regarding the design of Protocol 305: heterogeneity of the control treatment which might confound assessment of safety and effects on overall survival, lack of clarity as to whether HER2-positive patients would have received standard therapy (trastuzumab). FDA also provided information on the need for an NDA to contain data on drug-interactions and impact on the QT interval.

On Nov. 23, 2009, a pre-NDA meeting, was held to discuss the content of an NDA based on the results of Protocol 305, which demonstrated a statistically significant effect on overall survival and on the secondary endpoint, overall response rate, supported by the demonstration of durable objective tumor responses in single arm studies (201 and 211).

On March 30, 2010, Eisai submitted NDA 201-532. The application was assigned priority review on May 28, 2010 and filed on June 11, 2010, with an action goal date of September 30, 2010. On August 25, 2010, FDA notified Eisai that the review had been extended by 3 months based on submission of a major amendment, resulting in a new action date of December 30, 2010.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable per the review dated September 29, 2010. The microbiological assessment determined that sterility was maintained throughout the manufacturing process. Stability

testing supports an expiry of 48 months when stored at25 °C (77 °F) with excursions permitted to 15° – 30° C (59° -86° F).

Eribulin mesylate is (b) (4). It is a synthetic analogue of halichondrin B, isolated from the marine sponge *Halichondira okadai*. The manufacturing process involves a (b) (4) As noted in the background section of this review, CMC review staff had expressed concerns regarding the acceptability of the starting materials for this complex molecule. During the course of the review, the CMC review staff requested that the starting materials be modified to (b) (4). While appropriate specifications were provided for these new starting materials and the acceptance criteria were revised to limits supported by the nonclinical studies qualifying the impurities, the CMC reviewers determined that additional information should be provided post-approval. There are no outstanding issues that preclude approval and Eisai agreed to the post-marketing commitments requested by CMC review staff. These are summarized in section 13 of this summary review.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the nonclinical pharmacology/toxicology reviewer, Dr. Kotch, and the supervisory reviewers, Drs. Pilaro and Leighton that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval and that no additional pharmacology/toxicology studies are needed.

Specifically, Dr. Kotch concluded that "[T]he nonclinical data used to support this NDA were sufficient to determine the pharmacologic activity of eribulin mesylate, and provided a comprehensive toxicity profile in rats and a partial toxicity profile in dogs. These data also enabled an adequate assessment of genetic and reproductive/developmental toxicity, qualification of drug substance/product and a partial identification of potential clinical toxicities." Further, Dr. Kotch noted that "[B]ased on the levels of impurities that were qualified in the nonclinical testing, Eisai should adjust the acceptance criteria for the drug substance and drug product to levels that do not exceed qualification values." This information was communicated to the ONDQA staff and to Eisai, Inc., who revised the acceptance criteria as directed by FDA.

The application was supported by pharmacology studies conducted in human tumor xenograft models, safety pharmacology studies assessing effects on cardiac conduction, blood pressure and heart rate, CNS and respiratory function, and evaluation of eribulin mesylate neuropathy.

Toxicology studies included assessment of metabolism and excretion in rats and dogs, drug-interactions potentially mediated through inhibition of P-glycoprotein, repeat dose toxicology studies in Fischer 344 rats and beagle dogs, with chronic toxicology studies in rats and beagle dogs. The application also contained the results of genetic toxicology studies, an embryo-fetal development (EFD) study conducted during organogenesis in rats, and special toxicology

studies assessing the myelotoxicity of eribulin mesylate on murine, dog and human CFU-GM progenitor cells and hematologic toxicity in bone marrow mononuclear cells.

As noted by Dr. Kotch, drug exposure increased with dose in both rodents and dogs, however there were species differences in protein binding of eribulin mesylate, with the greatest degree of protein binding identified in humans. Eribulin mesylate is primarily cleared in the feces with at most 15% cleared renally. No major metabolites were identified in dogs and rats.

In a multiple dose toxicology studies, the primary targets of toxicity in both species (rats and dogs) were the hematopoietic organs (bone marrow, thymic and lymphoid tissue atrophy), the testes (degeneration) and the liver (necrosis, elevated AST, ALT and cholesterol). Eribulin mesylate is genotoxic, with positive findings demonstrated in the mouse lymphoma mutagenesis and the rat micronucleus assay. Given the indicated patient population (patients with metastatic breast cancer), carcinogenicity studies are not required for assessment of risks of this drug.

The EFD study demonstrated that eribulin mesylate is teratogenic in rats at doses less than half (42%) of the recommended dose of 1.4 mg/m^2. Fetal malformations were observed at doses of 0.15 mg/kg and embryo-lethality at doses at or above 0.10 mg/kg. In addition, toxicologic effects (early delivery, adverse clinical signs and/or enlarged spleens) were observed in dams at 0.15 mg/kg/day. Fetal malformations occurred at 0.15 mg/kg indicating E7389 has teratogenic potential.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The dose and schedule chosen for the major efficacy trial, Protocol 305, was based on the results of dose-finding, sequential dose-escalation studies and fixed-dose activity studies. Initial clinical investigations included four sequential, dose-escalation trials conducted to determine the maximum- tolerated dose (MTD) of eribulin mesylate that employed a weekly dosing schedule for three weeks of a 28-day treatment cycle, with eribulin administered either as an intravenous bolus or as a one-hour intravenous infusion. Based on these studies, single-arm, fixed dose (Phase 2) trials were initiated to investigate anti-tumor activity (objective response rate) that administered eribulin as a dose of 1.4 mg/m^2 as an intravenous (IV) bolus on days 1, 8, and 15 of a 28-day cycle. However, this regimen resulted in a higher than desired frequency of dose delays, doses withheld, and dose reductions due to Grade 3 and 4 neutropenia, resulting in an amendment of the treatment regimen to eribulin at a dose of 1.4 mg/m^2 IV bolus on days 1 and 8 of a 21-day cycle. This modified regimen was selected for use in the randomized, definitive efficacy trials.

Data from dense pharmacokinetic (PK) sampling from 125 patients enrolled into eight trials and sparse PK sampling from 211 patients enrolled into a single phase 2 trial were provided in the application. The pharmacokinetic profile of eribulin is characterized by a rapid distribution phase, followed by a longer terminal phase, with a geometric mean terminal phase half-life

was 37 hours to 43 hours. Exposure (area under the concentration vs. time curve ($AUC_{0\text{-}inf}$)] increases linearly over the dose range of 0.25 mg/m^2 to 4 mg/m^2, which incorporates the range of recommended doses contained in the Dosage and Administration section of the proposed product label. Eribulin exhibits protein binding of 49% to 65%, across various studies. There was no accumulation of eribulin observed with administration on the recommended weekly schedule.

The major elimination pathway of eribulin in animals and in humans is fecal (82% of the dose in humans) with renal elimination as a minor component (<9%), primarily through excretion of the intact drug. Eribulin is a substrate of P-glycoprotein (Pgp) and weak inhibitor of Pgp. Based on *in vitro* studies, the CYP3A4 enzyme is responsible for eribulin for <1% of hepatic metabolism (<1%) of eribulin. Drug studies showed that eribulin exposure (AUC) is not altered in a clinically meaningful way when co- administered with ketoconazole, a strong CYP3A4 inhibitor.

Population PK analyses did not identify any clinically meaningful effects of age, gender and race on the pharmacokinetic profile of eribulin.

The systemic exposure of eribulin was increased in patients with mild and moderate hepatic impairment, which is the basis for the recommended lower starting dose of eribulin of 1.1 mg/m^2 and 0.7 mg/m^2 for patients with mild and moderate hepatic impairment, respectively, in the package insert. Although renal elimination is minor (accounting for elimination of 9% or less of the administered dose), systemic exposure was increased by two-fold in patients with moderate renal impairment which is the basis for the recommended lower starting dose of eribulin of 1.1 mg/m^2 for patients with moderate renal impairment in the package insert and the rationale for the request for a required post-marketing study to further characterize the pharmacokinetic profile of eribulin in patients with severe renal impairment.

The effect of eribulin on the QT interval was assessed based on comparison of baseline to post-treatment ECGs obtained in a single dedicated study (Protocol 110) enrolling 26 patients who received the recommended dose of eribulin. Analysis of these data revealed that the maximum mean QTcF change from baseline is 11 msec with an upper bound of the 2-sided 90% confidence interval of 18 msec observed on Day 8 of the dosing cycle. The data were interpreted as suggesting a delayed effect of eribulin on QTc interval prolongation; while the magnitude of the delay is small, potential clinical effects cannot be ruled out and therefore this risk has been described in product labeling in the Warnings and Precautions section.

The clinical pharmacology review team concluded that exposure-response (E-R) relationships could not be established for clinical efficacy endpoints due to limited exposure data (n=211 patients) collected as sparse PK samples at the recommended dose and schedule.

Comments cited in the review, which do not preclude the approval of this application based on clinical pharmacology, will be conveyed to the applicant in correspondence under the IND. These recommendations provided by the clinical pharmacology reviewer for additional characterization of the pharmacology of eribulin include requests for

- Collection of sparse pharmacokinetic data from all subjects in future development programs. The purpose is to develop exposure response relationship for efficacy and safety endpoints to support proposed dosing recommendations and dose adjustments.
- Characterization of the predictive and/or prognostic relationship between β-tubulin, microtubule associated proteins, and Pgp mRNA expression in tumors within ongoing and future randomized, controlled trials.
- Collection of germline DNA to enable future pharmacogenetic analyses of eribulin response and tolerability (e.g. neuropathy) in ongoing and future clinical trials.
- Determination *in vitro* whether eribulin is a substrate and an inhibitor of BCRP, OATP1B1 and OATP1B3.
- Exploration of the mechanisms for the delayed effect on the QTc interval by performing a hERG trafficking study for parent and relevant metabolites with concurrent positive control like arsenic trioxide and pentamidine in further non-clinical testing.
- Exploration of the delayed effect on the QTc interval by performing a study to detect delay in distribution to myocardium in further non-clinical testing.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Data from study 305 serves as the primary basis for the efficacy evaluation. The supportive evidence of efficacy is provided in the integrated summary of efficacy, which was based upon pooled data from studies 305, 201, and 211. Only data from subjects who were treated with the same dose and schedule of eribulin proposed in the product label were used in the integrated efficacy analysis.

This NDA is primarily supported by data from a single, multicenter, open-label, randomized, active-controlled trial, E7389-G000-305: the EMBRACE Trial (**E**isai **M**etastatic **Br**east Cancer Study **A**ssessing Physician's **C**hoice Versus **E**7389). This trial was entitled "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 original protocol was finalized on April 26, 2006 and was amended four times:

- Aug. 8, 2006 (Amendment 1): Amended eligibility criteria to require that patients be refractory to the most recent chemotherapy regimen and that no systemic anticancer therapy could have been administered within 4 weeks prior to enrollment.
- January 4, 2008 (Amendment 2): Clarified baseline tumor assessment requirements.
- June 5, 2008 (Amendment 3): The patient sample size was increased from 630 to 1000 patients due to a slower than expected event rate.
- March 3, 2009 (Amendment 4): No substantive changes.

The primary objective of the study was to compare the overall survival (OS) of eribulin-treated patients with the overall survival of patients treated with treatment of physician's choice (TPC).

Secondary efficacy objectives included progression-free survival (PFS), objective tumor response rate (ORR), and duration of response. Safety objectives included characterization of the incidence of adverse events, use of concomitant medications and study drug exposure (descriptive statistics based on days of dosing/dose administered).

Key eligibility criteria included disease progression within six months of the most recent chemotherapy, prior treatment with an anthracycline and with a taxane unless such therapy was contraindicated, and treatment with at least two prior chemotherapy regimens for metastatic disease, with a maximum of five prior chemotherapeutic regimens. Patients were randomized (2:1) to receive eribulin or a single agent therapy chosen by their physician (designated by the applicant as the "Treatment of Physicians Choice," or "TPC"). Patients with any of the following were not eligible: pre-existing neuropathy of > grade 2 severity; radiation therapy encompassing > 30% of marrow; prior treatment with mitomycin C or nitrosurea; lymphangitic pulmonary involvement that resulted in pulmonary dysfunction requiring active treatment; CNS or subdural metastases, unless stable following treatment; anti-coagulant therapy with warfarin or related compounds; or severe/uncontrolled intercurrent illness.

Patients were randomized (2:1) to eribulin or single agent chemotherapy, hormonal therapy, biological therapy or best supportive care. Randomization was stratified by geographic region, HER2/neu status, and prior treatment with capecitabine.

Treatment Plan
Arm 1: eribulin mesylate 1.4 mg/m^2 intravenous push over 2-5 minutes on days 1 and 8 of each 21-day cycle. Dose delays and reductions for hematologic and non-hematologic toxicities (graded by NCI CTCAE ver. 3.0) were specified in the protocol and are reflected in proposed product labeling.

Arm 2 (TPC): any single agent chemotherapy, hormonal therapy, or biological therapy appropriate for treatment of breast cancer or best supportive care chosen by the treating physician prior to randomization. Dose modifications for single agents were to follow approved product labeling.

Study monitoring for tumor:
Baseline tumor assessments with MRI or CT scans of the chest, abdomen, pelvis, and any other areas of suspected disease, and photographs of target lesions in the skin, were to be conducted within four weeks prior to the start of study treatment. During study, radiographs and photographs of disease present at baseline were to be obtained every 8 weeks until disease progression. Patients who discontinued study treatment without progressive disease were assessed at time of termination of study treatment and every three months thereafter until

documentation of progressive disease or initiation of another anti-cancer therapy. All patients were followed every three months for survival following discontinuation of study therapy.

Bone scans were to be obtained within 6 weeks before to the start of study treatment and repeated only if clinically indicated.

Independent radiology reviews were performed by an independent imaging core laboratory (b) (4)) to assess tumor response and progression.

Statistical Analysis Plan:
The original statistical analysis plan specified a sample size of 630 patients (420 in eribulin and 210 in TPC) and a plan to conduct an interim analysis for efficacy or futility after 206 events (50% of the final events) and a final analysis of overall survival after 411 events (deaths).

The analysis plan was revised after an interim assessment revealed that the event rate was smaller than expected; the amendment resulted in an increase in sample size from 630 to 1000 patients. In the final analysis plan, the nominal significance level for the interim test was 0.003, and the nominal level of significance for the final analysis was 0.049, based upon the O'Brien and Fleming alpha spending function. The study was to be terminated for efficacy ($p<0.003$) or futility (if the interim analysis demonstrated a hazard ratio in which the lower limit of the 95% confidence interval for the hazard ratio of OS higher than 0.85).

RESULTS

Study 305 enrolled a total of 762 patients with locally recurrent or metastatic breast cancer who had received two to five prior chemotherapy regimens, including an anthracycline and a taxane. The study was initiated on November 16, 2006 (first patient visit) and enrolled patients from 135 sites in 19 countries. The Data Monitoring Committee recommended termination of the trial after the final analysis of overall survival; the data cut-off date used in the analyses presented in the application was May 12, 2009.

Sixty-four percent of patients were enrolled in North America, Western Europe, or Australia, 25% were enrolled in Russia and Eastern Europe, and the remaining 11% were enrolled in Latin America and South Africa. One hundred forty-six patients (19%) were enrolled from U.S. sites (100 patients randomized to eribulin and 46 to TPC).

Ninety-one percent of patients in Protocol 305 had an ECOG performance status of 0 or 1 at study entry. Tumor prognostic characteristics were similar between arms. The study population consisted of 67% ER positive patients, 49% PR positive patients, 74% HER2/*neu* receptor negative patients, with 19% of the population having triple negative (ER^-, PR^-, HER2/*neu*-) disease. The majority of patients (82%) had visceral disease, with 60% having hepatic metastases and 38% pulmonary metastases, while 61% had osseous metastases. Approximately half the patients had three or more sites of metastatic disease. The median number of prior chemotherapy regimens was four in each arm.

The Data Monitoring Committee conducted the pre-specified interim analysis of OS after 207 deaths (50% of the planned events) with a data cut-off date of August 23, 2008. Although the interim analysis crossed the pre-specified boundary (p 0.0018, Cox model) the DMC did not recommend study closure due to lack of mature data and evidence of an "apparent evolving difference in treatment effect on survival between the August 23, 2008 data and more recent IVRS data."

The final analysis of overall survival was conducted after 422 events and demonstrated a significant improvement in survival, crossing the pre-specified, adjusted boundary for a significant result (p-0.049, two-sided). The final analysis yielded a hazard ratio of 0.81[(95% CI: 0.66, 0.99); p-0.041; two-sided stratified log-rank test, stratified by HER2/*neu* status, prior capecitabine exposure, and geographical region]. The median overall survival was 2.5 months longer in the eribulin arm than in the control arm (13.1 months vs. 10.6 months). The FDA statistical reviewer confirmed that the findings were also significant in a sensitivity analysis conducted at 411 events as pre-specified in the statistical analysis plan.

The European Medicines Agency (EMA) requested that Eisai provide an updated analysis of overall survival results after approximately 75% of patient deaths occurred. At FDA's request, Eisai submitted the results of this updated, unplanned survival analysis, conducted after 589 deaths. This analysis demonstrated that the treatment effect on overall survival was persistent and consistent with the primary analysis. This updated survival analysis yielded a HR of 0.81 (95% CI 0.68, 0.96), nominal p=0.014, stratified log-rank test) and difference in median survival times of 2.7 months among eribulin-treated patients compared to the control arm. These updated results, which provide more mature information on the treatment effect compared to the prespecified analysis, are provided in the figure below and are also included in product labeling.

Overall Survival in eribulin-treated patients vs. Control Arm - Study 305

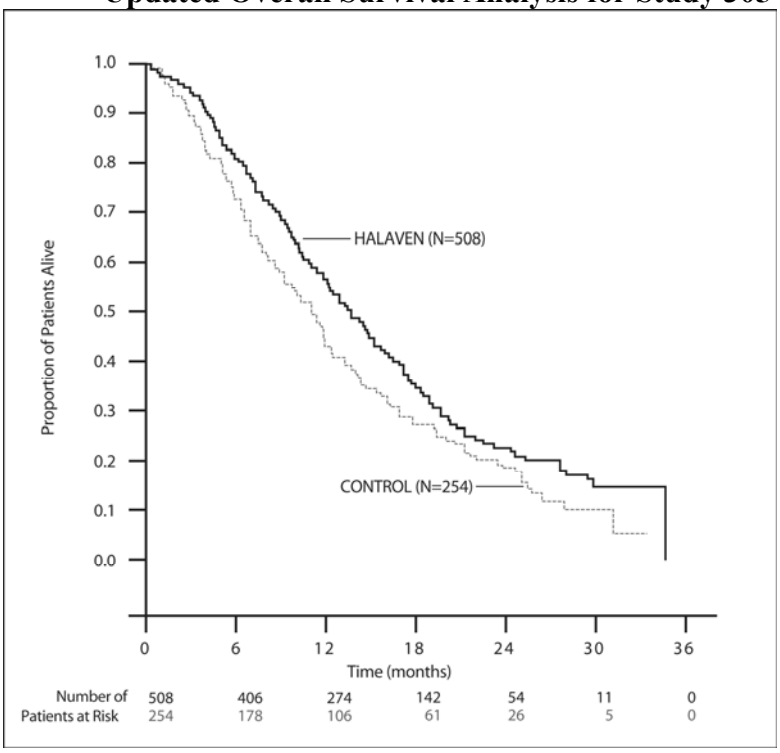
Overall Survival	Eribulin mesylate (n=508)	Control Arm (n=254)
Primary survival analysis		
Number of deaths	274	148
Median, months (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
Hazard Ratio (95% CI)[a]	0.81 (0.66, 0.99)	
P value[b]	0.041	
Updated survival analysis		
Number of deaths	386	203
Median, months (95% CI)	13.2 (12.1, 14.4)	10.6 (9.2, 12.0)

CI = confidence interval

[a] Based on 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.

Updated Overall Survival Analysis for Study 305



Secondary Efficacy Endpoints

There was no pre-specified statistical analysis plan for controlling the overall false postivie rate for the secondary endpoints. Without adjustment, Protocol 305 also demonstrated a higher objective response rate for patients in the eribulin arm compared to TPC (11.2% vs. 3.9%, nominal p=0.0006) based on independent review-determined response rates. Among responding patients in the eribulin arm, the median duration of response was 4.2 months (95% CI: 3.8, 5.0 months). These findings confirmed, and were consistent with, the objective response rates determine by the clinical investigators.

Progression-free survival as determined by independent review was not statistically significantly prolonged but favored the eribulin arm [HR 0.87 (95% CI: 0.71, 1.05), p=0.14] with median progression-free survival times of 113 days in the eribulin arm and 68 days in the TPC arm. This finding is consistent with the significant improvement in PFS based on investigator-determined disease progression [HR 0.76 (95% CI: 0.64, 0.90), p=0.002], with median PFS times of 110 days and 66 days in the eribulin and TPC arms, respectively. Differences in the results between the independent review and investigator-determined PFS reflected the large number of patients censored in the independent review assessment.

Supportive studies

The application also contained the results from two single-arm trials in patients with relapsed or refractory metastatic breast cancer (Protocols 201 and 211). These studies were originally

intended to support a request for accelerated approval, based on demonstration of durable objective responses (primary endpoint) in patients who had previously received an anthracycline and a taxane; therefore the primary analysis of response rates was based on independent reviewer assessment. Study 201 enrolled 104 patients; 71 of the 104 patients received eribulin at a dose of 1.4 mg/m^2 on days 1, 8, and 15 of a 28-day cycle and 33 received eribulin at a dose of 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle. All patients enrolled in Protocol 211 received eribulin at a dose of 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle.

Overall response determined by independent review were 11.5% (95% CI: 5.7%, 20.1%) and 9.3% (05% CI: 6.1%, 13.4%) with median durations of response of 171 and 126 days, in Protocols 201 and 211, respectively.

8. Safety

The safety database for eribulin mesylate was adequate to characterize the safety of this product for the proposed indication. Eribulin has been administered to 1,222 patients in open-label and active-controlled trials enrolling patients with various primary tumors; within the safety experience, there was safety data for 240 patients who received eribulin for at least 6 months. The safety database (n=1222) consisted primarily of women (82%) with a median age of 58 years (range: 26 to 91 years), who were Caucasian (83%). The safety database contained 5% Black, 2% Asian, and 5% other racial/ethnic groups.

The safety profile reported in the overall safety database was similar to that reported in eribulin-treated patients enrolled in Protocol 305. Since Protocol 305 was the largest completed clinical trial with an internal control, the adverse reactions for Halaven are best characterized in this study. In Protocol 305, patients were monitored for any adverse event (recorded on case report forms) from trial enrollment through 30 days after the last dose of study medication. Adverse reactions were categorized by severity grade using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3 or by the undefined terms of “mild”, “moderate” or “severe”.

The most common adverse reactions (≥25%) reported in the 503 eribulin-treated patients enrolled on Protocol 305 were asthenia/fatigue, neutropenia, alopecia, peripheral neuropathy, nausea, and constipation. The most serious adverse reactions were febrile neutropenia (4%) and neutropenia (2%). The incidence of serious adverse events were similar in the two groups (25% in each group) and the proportion of patients who died within 30 days of the last dose of study medication was lower for eribulin-treated patients compared to the control group (4.0 vs. 7.7%). The other major significant toxicity was peripheral neuropathy, which occurred in 36% of eribulin-treated patients and was the most common adverse event resulting in termination of eribulin treatment. In addition, 3% of eribulin-treated patients required dose reductions for peripheral neuropathy. Both sensory and motor neuropathy were reported and neuropathy was persistent (lasting more than one year) in 5% of eribulin-treated patients. These adverse reactions are appropriately described in product labeling with recommendations for pre-treatment assessment for neuropathy, a complete blood count prior to each dose, and recommendations for dose reduction in the event of toxicity.

Moderate increases (NCI CTC grade 2 or higher) in hepatic transaminases occurred in 18% of patients with normal or Grade 1 liver function tests at study entry; no Hy's Law cases were reported. The labeling provides directions for lower starting doses for patients with mild (1.1 mg/m^2) or moderate (0.7 mg/m^2) hepatic impairment.

The safety data from Protocol 305 are provided in the table below; these results were obtained from 750 patients enrolled in Protocol 305 who received at least one dose of study medication. There were 503 women with metastatic breast cancer who received eribulin at a dose of 1.4 mg/m^2 on Days 1 and 8 of a 21-day cycle and 247 women who received single agent anti-treatment chosen by their physician (control group). Treatment administered in the control group included vinorelbine (25%), gemcitabine (19%), capecitabine (18%), taxanes (15%), anthracyclines (10%), other chemotherapy (10%), and hormonal therapy (3%). The median duration of exposure to study treatment was 118 days for eribulin-treated patients and 63 days for patients in the control group.

Adverse Reactions with a Per-Patient Incidence of at Least 10% in Study 1

MedDRA ver 10.0	HALAVEN n=503		Control Group n=247	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and Lymphatic System Disorders [a]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[b]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders and administrative site conditions				
Asthenia/Fatigue	54%	10%	40%	11%
Mucosal inflammation	9%	1%	10%	2%
Pyrexia	21%	<1%	13%	<1%
Gastrointestinal disorders				
Constipation	25%	1%	21%	1%
Diarrhea	18%	0	18%	0
Nausea	35%	1%	28%	3%
Vomiting	18%	1%	18%	1%
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Investigations				
Weight decreased	21%	1%	14%	<1%
Metabolism and nutrition disorders				
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Cough	14%	0	9%	0
Dyspnea	16%	4%	13%	4%
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[c]	10%	NA[c]
Infections and Infestations				
Urinary Tract Infection	10%	1%	5%	0

[a] based upon laboratory data.
[b] includes neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[c] not applicable; (grading system does not specify > Grade 2 for alopecia).

The clinical pharmacology reviewer identified the need for a required post-marketing trial under 505(o) to further characterize the pharmacokinetics of eribulin in patients with severe renal impairment.

9. Advisory Committee Meeting

There were no controversial issues identified by the review team or me that would have benefitted from an advisory committee discussion. The division sought the advice of three ODAC members, individually. All three (two physicians and a patient advocate) considered

that the applicant had demonstrated a positive risk:benefit assessment which supported approval for the proposed indication.

10. Pediatrics

The Pediatric Review Committee (PeRC) conducted a review of the application on May 5, 2010; the PeRC concurred with the recommendation by the review division that a waiver of the requirements under the Pediatric Research Equity Act as requested by the applicant was appropriate, given the rarity of breast cancer in the pediatric population (0-18) which renders conduct of the necessary studies to be impossible or highly impracticable.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

Five clinical sites (two in the U.S. and three ex-US sites) were chosen for auditing of clinical study data by FDA's Division of Scientific Integrity (DSI); sites were selected based on the number of patients enrolled, number of protocol deviations, and differential response rate between the eribulin and TPC arms. As per routine, DSI also inspected the applicant (Eisai Europe Ltd.) and the contract research organization responsible for the independent assessment of tumor-based endpoints in Study 305 (b) (4)). The inspectional findings revealed no significant deviations that would preclude the use of the clinical data provided in support of this NDA.

The NDA contained a statement in each clinical study report, attesting that the trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. Financial disclosure information for protocol 305 study investigators was included in the application. There were no financial conflicts of interest identified by any investigator as defined in 21 CFR 54.2(a), (b), and (f).

12. Labeling

- Proprietary name: I concur with the decision of the DMEPA (Carol Holquist) who determined that the proprietary name of Halaven Injection was conditionally acceptable on July 2, 2010.

- Physician labeling
  All consultant and reviewer recommendations for product labeling were considered in internal labeling discussions. The rationale for rejection of labeling recommendations by DDMAC and MHT reviewers were verbally provided at these meetings. In addition, separate meetings were held with MHT, SEALD, and DBOP staff regarding introduction of new subsections in the Warnings and Precautions for women and men

of childbearing potential. DBOP staff noted medical subspecialists in the treatment of cancer patients are well aware of the potential for embryofetal toxicity with anti-neoplastic agents and routinely extrapolate the risks cited in the Pregnancy subsections in Warnings and Precautions and in Use in Specific Populations when counseling men and women of childbearing potential. Inclusion of a separate subsection would "dilute" the impact of other significant risks.

- Indication revised to reflect the population enrolled in Protocol 305: this population was limited to patients with metastatic disease (no locally advanced disease patients) and prior treatment with an anthracycline or taxane may have occurred in the adjuvant or neoadjuvant setting.
- Dosage and Administration section revised to include reduced initial doses in patients with hepatic and renal impairment based on pharmacokinetic data included in the application; revised the dose modification section to include specific numbers rather than NCI CTC grades (which has been revised); remove (b) (4) as this was not needed for safe use; shortened description of preparation for use for brevity and clarity.
- Contraindications: Removed the contraindication for patients with (b) (4) in accordance with FDA/CDER policy as this is a theoretical risk that has not been reported.
- Warnings and Precautions
  - Added a new subsection, "QT Prolongation" based on serial ECGs obtained in Protocol 305 and other clinical studies.
  - Deleted proposed subsection (b) (4) adequate directions for dosing provided in Dosage and Administration section.
  - Retitled section 5.3 from (b) (4) and replaced with "Embryofetal Toxicity" as this term more accurately characterizes this risk. In accordance with FDA policy, the term "Pregnancy Category D" moved to section 8.1 and data regarding nonclinical studies moved to sections 8.1 and 13.
  - Retitled section 5.1 from (b) (4) to the more specific "Neutropenia"; added data from Protocol 305 characterizing risks; removed detailed statements regarding (b) (4) in the D&A section.
  - Retitled section 5.4 from (b) (4) to the more descriptive term "Peripheral Neuropathy" and revised this subsection to include data on the risks observed with cross-references to the D&A section.
- Adverse Reactions
  - Added references to Warnings and Precautions for peripheral neuropathy and QT prolongation.
  - Revised table of adverse events to include hematologic adverse events based on laboratory data to the primary table in this section, re-ordered events in the table from most to least common, combined the NCI CTC Grades 3 and 4 adverse reaction rates into a single column.
  - Deleted uninformative statement on (b) (4)

- Drug Interactions
  - Section 7.2 modified to provide greater detail regarding extent of testing for eribulin inhibition of specific cytochrome enzymes
- Use in Specific Populations
  - The applicant's proposed labeling was limited to a reference to the Warnings and Precautions subsection entitled Pregnancy Category D. The final labeling contains a summary of the nonclinical data and characterizes the risks seen relative to the recommended dose in humans. Did not include information under subsection 8.1.
  - The labeling was revised to provide data in the appropriate population (patients greater than or equal to 65 years of age) rather than (b) (4) as proposed by the applicant, in accordance with FDA Guidance for characterizing data in geriatric patients.
  - Subsection on renal impairment revised to include results of population PK analyses indicating altered clearance in patients with moderate renal dysfunction and to reference specific dosing recommendations in this population.
  - Subsection on hepatic impairment modified to include information on the number of subjects studied in subpopulations.
- Overdosage
  - Editorial changes and deletion of information based on medical management which is general in nature and not specific to the drug.
- Description
  - Deletion of promotional language ((b) (4)).
- Clinical Pharmacology
  - Deletion of information in section 12.1 of information claims not supported by substantial evidence regarding (b) (4)
  - Addition of data under section 12.2 (information proposed by application under subsection in 12.3) regarding the results of the dedicated QT study in patients characterizing treatment effects of eribulin on cardiac electrophysiology (as captured in standard ECGs)
  - Deletion of potentially misleading or promotional language from section 12.3 (e.g., (b) (4) and replaced where necessary with specific data. Metabolism subsection revised to include additional details on evaluation of metabolism by cytochrome enzymes. Revised subsection on "effects on age, gender, and race" to clarify that the effects observed are not clinically meaningful (rather than the vague description, (b) (4)).
- Nonclinical Toxicology
  - Minor revisions to provide context for doses administered to animals in which effects were seen by providing an estimate of the fraction/multiple of the recommended human dose.
- Clinical Studies

        - Removed tabular presentation of patient demographics/baseline entry characteristics and provided data in text.
        - Provide additional description of the agents administered in the control arm.
        - Included results of updated survival analysis in tabular form and as a figure (Kaplan-Meier curves) in order to provide the most complete information regarding treatment effects to healthcare providers. Since this was not a planned analysis but one provided upon request of the regulatory authority, no tests for statistical significance are included in labeling.
        - Supportive data based on objective response rate and duration of response in eribulin-treated patients included for informational purposes.
    - (b) (4) deleted in accordance with current FDA policy on labeling.
    - Patient Counseling
        - Editorial revisions

- Carton and immediate container labels
  Revisions to carton/container labeling were incorporated by the application as requested in the 9/10/10 consult review from Loretta Holmes (DMEPA).

- Patient labeling/Medication guide
  The review team determined that there were no unusual safety risks for product in the indicated patient population that warranted a Medication Guide to mitigate risks. The toxicities of this product are similar to other traditional chemotherapeutic agents. Although the applicant (Eisai) submitted patient labeling, the clinical reviewer did not believe such labeling is necessary to ensure safe use.

  The content and format of the applicant's proposed patient labeling were edited for consistency with applicable regulations and policy for patient labeling by DRISK (Sharon Mills) and for accuracy by the clinical reviewer, based on the safety and efficacy data provided in the application. I concur with these edits.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend that this NDA be approved for the following indication:

  "HALAVEN is indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting."

- Risk Benefit Assessment

All members of the review team recommended approval of this application. The demonstration of an improvement in overall survival provides both evidence of efficacy and adequate characterization of safety in support of approval. The indicated population has an unmet medical need and has already accepted the risks of cytotoxic chemotherapy, as demonstrated by the 2-5 prior chemotherapy regimens administered to patients in the primary efficacy study and their acceptance of alternative chemotherapy regimens in the control arm.

The demonstration of an effect on survival is considered robust based on the consistency of the finding across relevant subgroups based on patient demographics and tumor prognostic characteristics and the demonstration of statistically significant effects on overall survival at multiple timepoints (interim analysis, final analysis, and updated analyses). Finally, efficacy is supported by evidence of anti-tumor activity [improvement in (investigator-determined) progression-free survival in Protocol 305 and evidence of durable objective tumor responses in Protocols 305, 211, and 201].

The overall results of this trial, in which 80% of patients were enrolled outside the U.S., can be extrapolated to the U.S. population. The practice of medical care for the treatment of metastatic breast cancer is generally well-standardized, particularly across North America, Western Europe, and Australia; this is reflected by the choice of treatment in the control arm, in that all agents are commonly used for treatment of multiply relapsed metastatic breast cancer. In exploratory subgroup analyses, treatment effects were driven primarily by the North America, Western Europe, and Australia, which enrolled the majority of the patients.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendation by the clinical review team that a REMS is not required for this product for the requested indication. When administered in accordance with product labeling, it is anticipated that the risks of Halaven will be tolerable and manageable. There are no unusual risks which required training to assure safe use, given that cytotoxic therapy are generally prescribed and administered only by healthcare professionals with specific training and experience in medical oncology and use of agents with similar toxicities.

- Recommendation for other Postmarketing Requirements and Commitments

  PMR 1689-1:
  "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."

Rationale for required PMR: Population PK data indicate that exposure is increased in patients with moderate renal function and that dose adjustments are needed to reduce the potential increased risk of eribulin-induced toxicity (neutropenia). Inadequate data are provided in the application to (b) (4) .

PMC 1689-2:
"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."

Rationale for PMC: The results of this study will provide more complete information on the efficacy of eribulin in the indication population.

PMC 1689-3:
"To submit a final report for the 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 report will include a subset analysis of overall survival in patients that progressed while on treatment with a taxane or other microtubule inhibiting agent, in addition to all protocol-specified analyses."

Rationale for PMC: The results of this study will provide more complete information on the efficacy of eribulin in the indication population. In addition, it will provide data on efficacy in population subsets of interest in whom efficacy may be diminished relative to the general population.

PMC1689-4:
To provide a single Chemistry, Manufacturing and Controls (CMC) Prior Approval Supplement (PAS) containing data further characterizing the starting materials for eribulin mesylate synthesis.

Rationale for PMC: The CMC review team determined that the proposed starting materials in the NDA were not acceptable and reached agreement during the review on (b) (4) starting material. These data will provide additional characterization of new starting materials which were not available in the NDA. Such data will be necessary to evaluate proposed future manufacturing changes under this NDA.

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/s/

PATRICIA KEEGAN
11/11/2010