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APPLICATION NUMBER:

201532

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201532

NDA APPROVAL

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

Dear Ms. Petraglia:

Please refer to your New Drug Application (NDA) dated March 30, 2010, received March 30, 2010, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Halaven (eribulin mesylate) Injection, 0.5mg/mL (1.0 mg/2 mL solution).

We acknowledge receipt of your amendments dated March 30, April 2, May 11, May 17, May 21, June 7, June 17, June 22, June 28, June 29, July 23, July 28 (2), August 9 (2), August 12, September 10 (2), September 16, September 23, September 24, September 28, September 30 (2), October 6, October 13, October 14, October 22, October 27, October 29 and November 11, 2010.

This new drug application provides for the use of Halaven (eribulin mesylate) Injection 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.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (package insert, patient information) Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.
The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 201532**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Halaven was not referred to an FDA advisory committee because there were no controversial issues that would have benefitted from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since breast cancer is rare in the 0-18 year old age group.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected, serious risk of increased toxicity in patients with impaired renal function.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased toxicity in patients with impaired renal function.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

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.

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

Final Protocol Submission:	December 31, 2010
Trial Completion Date:	June 30, 2012
Final Report Submission:	December 31, 2012

Submit the protocol to IND 67193, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated September 30, 2010. These commitments are listed below.

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..

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.

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. 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 31, 2012
Final Report Submission: February 28, 2013.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment in your submission dated September 17, 2010. This commitment is listed below.

PMC1689-4:

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

Submit clinical protocols to IND 67193 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.
Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling [including Patient Labeling (PPI)]
Carton and Container Labeling